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#29

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**US 5,674,860**
Issued:	**October 7, 1997**
To:	**Christer Carl Gustav Carling; Jan William Trofast**
For:	**Combination of a Bronchodilator and a Steroidal Anti-Inflammatory Drug for the Treatment of Respiratory Disorders**

I hereby certify that this paper is being deposited with the United States Patent and Trademark Office via hand delivery on September 19, 2006.

RAMEL CARRINGTON

Name of person depositing the paper and fee

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APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

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Exhibits

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. § 156

Sir:

Applicant, AstraZeneca AB, a corporation organized and existing under the laws of Sweden, the address of which is S-151 85 Södertälje, Sweden, represents that it is the owner and assignee of the entire interest in and to Letters Patent of the United States No. 5,674,860 (attached hereto as Exhibit A), granted to Christer Carl Gustav Carling and Jan William Trofast on the 7th day of October, 1997, for "Combination of a Bronchodilator and a Steroidal Anti-Inflammatory Drug for the Treatment of Respiratory Disorders," by virtue of assignment from Christer Carl Gustav Carling and Jan William Trofast to Aktiebolaget Astra, recorded December 17, 1992, at Reel 6378, Frame 0021; and from Aktiebolaget Astra to Astra Aktiebolaget, recorded June 9, 1997, at Reel 008546, Frame 0050. AstraZeneca AB is the successor company to Astra Aktiebolaget after its merger with Zeneca Group PLC in 1999.

The Approved Product that is relevant to this application is Symbicort® Inhalation Aerosol, which was approved in two dosage strengths: Symbicort 80/4.5 [budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg)]; and Symbicort 160/4.5 [budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg)], collectively "Symbicort" or "Approved Product."

The holder of marketing approval for Symbicort is AstraZeneca Pharmaceuticals LP. The NDA holder and patent owner, AstraZeneca Pharmaceuticals LP and AstraZeneca AB, respectively, are both owned by AstraZeneca PLC, headquartered in London, England.

Applicant, through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. § 156 by providing the following information required by the statute, 35 U.S.C. §156(d), and by the Rules of Practice in Patent Cases, 37 C.F.R.

§ 1.740. For the convenience of the United States Patent and Trademark Office ("USPTO"), the information in this application is presented in the order set forth in Section 1.740 of the Rules.

1. Identification of the Approved Product (37 C.F.R. § 1.740(a)(1))

The Approved Product is Symbicort, a combination of budesonide and formoterol fumarate dihydrate for oral inhalation in two different dosage strengths (approved label attached as Exhibit B). The two dosage strengths of Symbicort each deliver the same amount of formoterol fumarate dihydrate (4.5 mcg) but different amounts of budesonide (80 and 160 mcg, respectively).

Pursuant to 37 C.F.R. § 1.740, the chemical and generic name, physical structure or characteristics of the Approved Product, Symbicort, are as follows:

The chemical name of budesonide is (RS)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity.

The chemical name for formoterol fumarate dihydrate is (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. Formoterol fumarate is a long-acting selective $ß_2$-adrenergic agonist ($ß_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator.

Symbicort is furnished in 10.2 g canisters and is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing 120 actuations. After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg (budesonide micronized/ formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the

lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. Symbicort also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

2. Identification of Federal Statute Under Which Regulatory Review Occurred (37 C.F.R. § 1.740(a)(2))

The Approved Product is a drug product and the submission was approved under Section 505(b) of the Federal Food, Drug, and Cosmetic Act ("FFDCA") (21 U.S.C. § 355(b)).

3. Identification of Date on Which Approved Product Received Permission for Commercial Marketing or Use (37 C.F.R. § 1.740(a)(3))

The Approved Product received permission for commercial marketing or use in a letter dated July 21, 2006, signed by Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary and Allergy Products, Office of Drug Evaluation II, Center for Drug Evaluation and Research, U.S. Food and Drug Administration. A copy of the approval letter is attached as Exhibit C.

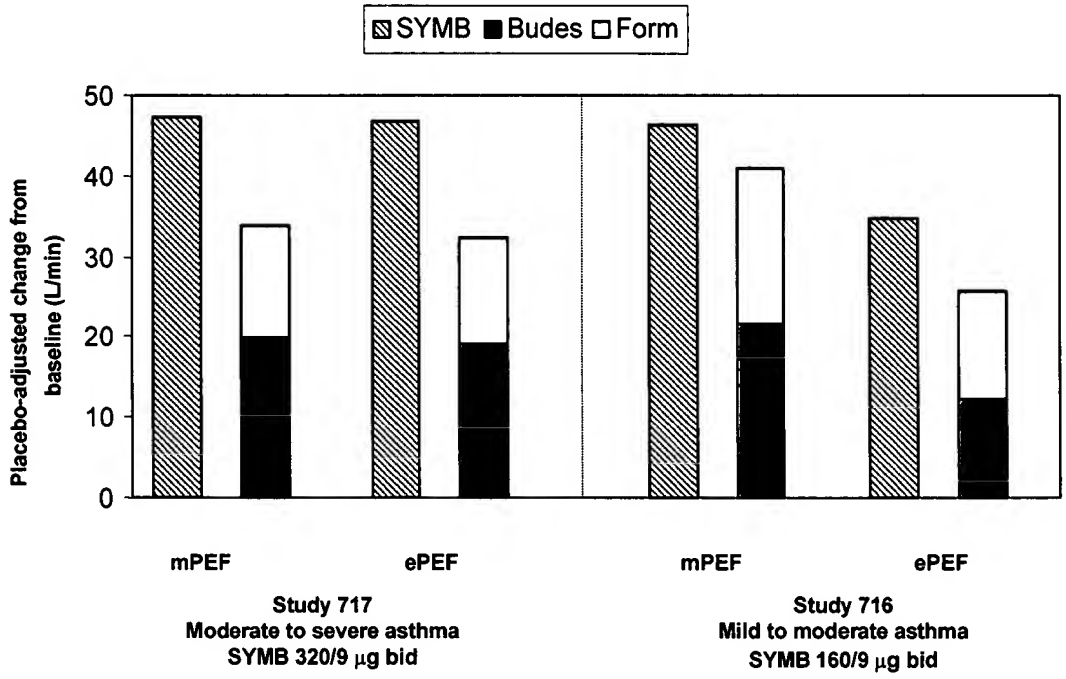
4. Identification of Active Ingredient (37 C.F.R. § 1.740(a)(4))

Symbicort has been approved under Section 505(b) of the FFDCA for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Symbicort is the first approved product that contains the combination of budesonide and formoterol fumarate dihydrate, which are shown to have a synergistic effect and a pharmacological interaction, as discussed in Exhibit D attached hereto. Accordingly, consistent with Section 2751 of the Manual of Patent Examining Procedure, Symbicort should be considered to have a new single active ingredient which has not been previously approved for commercial marketing and use.

Clinical evidence of the synergistic effect seen with budesonide and formoterol administered as Symbicort is best illustrated by the results of two pivotal US studies that form the basis of the approval of NDA 21-929 for Symbicort (Figure 1).

Figure 1 **Morning and evening PEF: placebo-adjusted change from baseline to the average during double-blind treatment (Studies 717 and 716)**



SYMB -SYMBICORT pMDI; Budes - budesonide pMDI (320 µg bid Study 717, 160 µg bid Study 716); Form - formoterol TBH (9 µg bid)
mPEF - Morning peak expiratory flow; ePEF - Evening peak expiratory flow; bid - Twice daily.

Applicant's Studies 716 and 717 were the first studies designed to demonstrate the effects of each separately administered monoproduct, budesonide ("Budes") and formoterol fumarate dihydrate ("Form"), in comparison to the combination product Symbicort ("Symb"), in two different treatment populations. As shown in Figure 1, as measured by the morning and evening Peak Expiratory Flow (PEF) in both studies, the effect of each monoproduct is less than half of the effect seen with Symbicort. Symbicort, therefore, produces in two different treatment populations a synergistic effect that is greater than the additive effect of each compound alone. A more detailed discussion, as well as additional preclinical and clinical data in support of the

synergistic effect of Symbicort, are set forth in Exhibit D and the two Declarations attached thereto that were submitted under 37 CFR § 1.132 by one of the inventors, Dr. Jan William Trofast, during the prosecution of the '860 patent application.

In addition, the two active ingredients in Symbicort are shown to have a pharmacological interaction that produces unexpectedly beneficial results. One example, as discussed further in Exhibit D, is the effect of the administration of budesonide on tolerance to formoterol, as seen in asthmatic patients. Long-term treatment with a formoterol monoproduct, a long-acting β_2-agonist bronchodilator, can result in tolerance to the drug. Concurrent maintenance treatment with budesonide in conjunction with formoterol has been shown to eliminate this tolerance and, in patients taking chronic formoterol monotherapy, tolerance may be reversed upon administration of budesonide during an acute episode of bronchoconstriction. Such results demonstrate that there is pharmacological interaction between the two administered drugs, formoteral and budesonide, that is observed as a beneficial effect of the combination.

The component active ingredients of the Approved Product have each been separately approved for marketing and use by the U.S. Food and Drug Administration ("FDA"). FDA-approved products containing budesonide include Entocort®, Pulmicort®, and Rhinocort® (all marketed by AstraZeneca). An FDA-approved product containing formoterol is Foradil® (marketed by Novartis). No other combination containing either of these active ingredients has been approved.

5. Timely Filing of This Application (37 C.F.R. § 1.740(a)(5))

This application is timely filed, pursuant to 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f), within the permitted sixty-day (60-day) period that began on July 21, 2006, the date

the product received permission under 21 U.S.C. § 355(b), and that will expire on September 19, 2006.

6. Identification of the Patent for Which an Extension Is Sought (37 C.F.R. § 1.740(a)(6))

Inventors:	**Christer Carl Gustav Carling and Jan William Trofast**
Patent No.:	**5,674,860**
Issued:	**October 7, 1997**
Expiration:	**October 7, 2014**

7. Copy of Patent Attached (37 C.F.R. § 1.740(a)(7))

A copy of US 5,674,860, for which an extension is being sought, is attached in its entirety as Exhibit A. This patent is due to expire on October 7, 2014, based on 35 U.S.C. § 1.54(c)(1), which provides for a 17-year patent term for a patent that issued from an application filed on or before June 8, 1995.

8. Disclaimers, Certificates of Correction, Receipts of Maintenance Fee Payment or Reexamination Certificate (37 C.F.R. § 1.740(a)(8))

No Certificates of Correction or Reexamination Certificates have been issued by the USPTO, and no Disclaimers have been filed by Applicant, for the referenced patent. Statements showing payment of the maintenance fee for pay years 04 and 08 are attached as Exhibit E. The maintenance fee payment for pay year 12 is not yet due.

9. Statement of Patent Claim Coverage of Approved Product (37 C.F.R. § 1.740(a)(9))

US 5,674,860 claims the Approved Product and methods of using the Approved Product, as shown in Exhibit F. Exhibit F presents a chart showing each applicable patent claim (claims 1, 3-5, 9, 11-13, 17-19, 22, 23, 25-29, 32, 33, 35, and 36) and the manner in which each such

applicable patent claim reads on the Approved Product or method of using the Approved Product.

10. Statement of Relevant Dates and Information Pursuant to 35 U.S.C. § 156(g) (37 C.F.R. § 1.740(a)(10))

In accordance with 37 C.F.R. § 1.740(a)(10), the content of this section is provided on a new page.

NDA 21-929 was submitted and approved for Symbicort. The relevant dates are as follows:

a. Effective Date of the Investigational New Drug (IND) Application: November 4, 2001

b. IND Number: 63,394

c. Date on which the NDA was initially submitted: September 23, 2005

d. NDA Number: 21-929

e. Date on which the NDA was approved: July 21, 2006

11. Brief Description of Significant Activities Undertaken by Marketing Applicant During Applicable Regulatory Review Period and Respective Dates (37 C.F.R. § 1.740(a)(11))

In accordance with 37 C.F.R. § 1.740(a)(11), the content of this section is provided on a new page.

Attached as Exhibit G is a brief description of the significant activities undertaken by the Applicant with respect to Symbicort during the applicable regulatory review period with respect to the Approved Product from November 4, 2001, to July 21, 2006.

12. Statement of Eligibility for Extension (37 C.F.R. § 1.740(a)(12))

In accordance with 37 C.F.R. § 1.740(a)(12), the content of this section is provided on a new page.

Applicant believes that US 5,674,860 is eligible for extension under 35 U.S.C. § 156 because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. § 156(a), 37 C.F.R. § 1.720

US 5,674,860 claims a drug product and a method of using that product.

b. 35 U.S.C. § 156(a)(1)

The term of US 5,674,860 will not have expired before submission of this application.

c. 35 U.S.C. § 156(a)(2)

The term of US 5,674,860 has never been extended under 35 U.S.C. § 156(e)(1) before submission of this application.

d. 35 U.S.C. § 156(a)(3)

This application for extension is submitted by an attorney for the owner of record in accordance with the requirements of 35 U.S.C. § 156(d)(1)-(4) and rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. § 156(a)(4)

The Approved Product, Symbicort, has been subject to a regulatory review period before its commercial marketing or use.

f. 35 U.S.C. § 156(a)(5)(A)

The commercial marketing or use of the Approved Product, Symbicort, is the first permitted commercial marketing or use of the product under the FFDCA (21 U.S.C. § 355(b)), pursuant to which such regulatory review period occurred. In this regard, the combination of budesonide and formoterol fumarate dihydrate as a new active ingredient required full scientific review by the FDA. (See Section 4.)

g. **35 U.S.C. § 156(c)(4)**

No other patent has been extended for the same regulatory review period for the Approved Product, Symbicort.

13. Statement as to Length of Extension Claimed and the Determination of Such Extension (37 C.F.R. § 1.740(a)(12))

In the opinion of the Applicant, US 5,674,860 is entitled to an extension of 1011 days, pursuant to 35 U.S.C. § 156 and the implementing regulations, based upon the regulatory review period for Symbicort.

The claimed length of this extension of 1011 days was determined pursuant to 37 C.F.R. § 1.775 as follows:

(1) The regulatory review period under 35 U.S.C. § 156(g)(1)(B), which began on November 4, 2001, and ended on July 21, 2006, and lasted 1721 days, the sum of computations in (a) and (b) below:

(a) The period of review under 35 U.S.C. § 156(g)(1)(B)(i) began on November 4, 2001, and ended on September 22, 2005, a period of 1419 days (including the last date); and

(b) The period of review under 35 U.S.C. § 156(g)(1)(B)(ii) began on September 23, 2005, and ended on July 21, 2006, a period of 302 days (including the last date);

(2) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 13(1) above (1721 days) less

(a) The number of days in the regulatory review period which were on or before the date on which the patent issued, October 7, 1997, which is zero (0) days, and

(b) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(c) One-half the number of days determined in subparagraph 13(1)(a) (1419 days) after subtracting the number of days determined in subparagraph 13(2)(a) zero (0) and (b) zero (0), or 709 days, which leaves 1011 days (1721 days - 0 days - 0 days - 709 days);

(3) The number of days as determined in subparagraph 13(2) in its entirety (1011 days), when added to the original term of the patent (October 7, 2014), would result in the date July 14, 2017;

(4) Fourteen (14) years when added to the date of approval (July 21, 2006) would result in the date July 21, 2020;

(5) The earlier date as determined in subparagraphs 13(3) and 13(4) is July 14, 2017;

(6) Since the original patent issued after September 24, 1984, five (5) years are added to the original expiration date of the patent (October 7, 2014), resulting in a date of October 7, 2019; and

(7) The earlier of the dates obtained in subparagraph 13(5) and in subparagraph 13(6) is July 14, 2017.

Therefore, the length of extension of patent term claimed by applicant is 1011 days, which is the period of time needed to extend the original expiration of term of October 7, 2014, until July 14, 2017.

14. Statement of Acknowledgment of Duty to Disclose Material Information (37 C.F.R. § 1.740(a)(13))

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to the determination of entitlement to the extension sought in this application.

15. Prescribed Fee (37 C.F.R. § 1.740(a)(14))

Please charge the necessary fee in the amount of $1,120.00, as prescribed in 37 C.F.R. § 1.20(j), and any additional fees which may be required, to Deposit Account 23-1703.

16. Contact Information (37 C.F.R. § 1.740(a)(15))

All inquiries and correspondence relating to this application for patent term extension should be directed to:

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17. Copies Enclosed (37 C.F.R. § 1.740(b))

Five duplicate copies of the present application papers are enclosed. The undersigned patent attorney certifies under penalty of perjury that the attached duplicates of the application papers are true and correct copies of such papers.

Dated: Sept. 19, 2006

Respectfully submitted,

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US005674860A

United States Patent [19]

Carling et al.

[11] Patent Number: 5,674,860

[45] Date of Patent: Oct. 7, 1997

[54] **COMBINATION OF A BRONCHODILATOR AND A STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS**

[75] Inventors: **Christer Carl Gustav Carling**, Dalby; **Jan William Trofast**, Lund, both of Sweden

[73] Assignee: **Astra Aktiebolag**, Sodertalje, Sweden

[21] Appl. No.: **317,407**

[22] Filed: **Oct. 3, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 992,089, Dec. 17, 1992, abandoned.

[30] **Foreign Application Priority Data**

Dec. 18, 1991 [EP] European Pat. Off. 91311761

[51] **Int. Cl.**[6] **A61K 31/56**; A61K 31/135

[52] **U.S. Cl.** **514/171**; 514/174; 514/653; 514/826

[58] **Field of Search** 514/171, 174, 514/653, 826

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,983,233	9/1976	Brattsand et al.	514/174
3,994,974	11/1976	Murakami et al.	564/170

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0416950	3/1991	European Pat. Off. .
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Jean H. Marsac, "Inhaled beta agonists and inhaled steroids in the treat. of asthma", Ann. of Allergy, 63(3), Sep. 1989, pp. 220–224.
Nils Svedmyr, "The current place of beta agonists in the mngmt. of asthma", Lung (USA), 168 no. supp, 1990, NY pp. 105–110.

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—White & Case

[57] **ABSTRACT**

Effective amounts of formoterol and/or a physiologically acceptable salt and/or solvate thereof and budesonide are used in combination for simultaneous, sequential or separate administration by inhalation in the treatment of an inflammatory respiratory disorder, such as asthma.

36 Claims, No Drawings

COMBINATION OF A BRONCHODILATOR AND A STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS

This application is a continuation of application Ser. No. 07/992,089 filed Dec. 17, 1992 now abandoned.

FIELD OF THE INVENTION

This invention relates to improvements in the treatment of mild as well as severe asthma and other respiratory disorders. More particularly, it relates to the use of a bronchodilator in combination with a steroidal anti-inflammatory drug for the treatment of respiratory disorders such as asthma, and to pharmaceutical compositions containing the two active ingredients. It emphasizes the use of a long-acting bronchodilator which provides rapid relief of symptoms.

BACKGROUND OF THE INVENTION

There have recently been significant advances in our understanding of asthma. Despite many advances, both in awareness of the disease by doctors and patients alike, coupled with the introdction of very powerful and effective anti-asthma drugs, asthma remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the most important feature of asthma. Recently there has been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving irreversible narrowing of the airways and fibrosis of the lung tissue. Therapy should therefore be aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

The most common cause for poor control of asthma is poor compliance with the long-term management of chronic asthma, particularly with prophylactic treatments, such as inhaled steroids, which do not give immediate symptom relief. Patients will readily take β_2-agonist inhalers, since these provide rapid relief of symptoms, but often do not take prophylactic therapy, such as inhaled steroids, regularly because there is no immediate symptomatic benefit. They also counteract down regulation of β_2-adrenoceptor agonists.

Formoterol, (N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl] formamide), is an adrenoceptor agonist which selectively stimulates β_2-receptors, thus producing relaxation of bronchial smooth muscle, inhibition of the release of endogenous spasmogens, inhibition of oedema caused by endogenous mediators, and increased mucociliary clearance. Inhaled formoterol fumarate acts rapidly, usually within minutes which gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of both β-agonist and steroid. Inhaled formoterol also exerts a prolonged bronchodilation, which in clinical trials has been demonstrated as up to 12 hours.

Budesonide, (16,17-butylidenebis(oxy)-11, 21-dihydroxypregna-1,4-diene-3,20-dione), may be given in a high inhaled dose (up to 2 mg daily) with very low systemic effects, possibly because of its rapid metabolism. The high rapid systemic elimination of budesonide is due to extensive and rapid hepatic metabolism. Long term clinical studies have shown that inhaled budesonide is a pharmacologically safe drug. High doses of inhaled budesonide are

highly effective and well tolerated when used in oral steroid replacement therapy. Budesonide represents a logical safe and effective therapy for long term control of asthma.

The inhaled route of administration enables the dose to be delivered directly to the airways. By this type of administration, it is possible to give a small dose and thereby minimizing unwanted side-effects. The drawbacks of the currently available bronchodilators are their relatively short duration of action. By using a compound with long duration e.g. formoterol it would be possible to avoid the nocturnal asthma, which so often causes considerable anxiety and debility to the patients. Formoterol gives less nocturnal waking than the commonly used short-acting agonists like salbutamol, terbutaline and the like. Formoterol has been registered for oral administration in Japan since 1986.

Pharmaceutical combinations of long-acting β_2-agonists and steroids are disclosed in two European applications, EP 416950 which discloses the combination of salmeterol and beclomethasone, and EP 416951 which discloses the combination of salmeterol and fluticasone propionate.

In Ann. Allergy 1989, 63 (3), p. 220–224 the use of a β_2-agonist, i.e. formoterol and a steroid, i.e. budesonide separately are mentioned. Not disclosed is a pharmaceutical combination including both formoterol and budesonide, or the use of the two compounds in combination therapy. The use of a β_2-agonist and a steroid separately is also mentioned in Lung (1990), 168, no. supp, p. 105–110.

OUTLINE OF THE INVENTION

The present invention is based on the concept of a novel combination therapy whereby formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation. This combination has not only a greater efficiency and duration of bronchodilator action but the combination also has a rapid onset of action. This new feature is of utmost importance in order to establish a higher compliance for patients and it provides a rescue medicine thereby avoiding the necessity for the patient of carrying two different inhalers. This simplifies life for patients considerably and makes life more comfortable and secure. The rapid onset of the long-acting β_2-agonist gives the patient immediate confirmation that he has taken an adequate dose and thereby avoiding overdosing of both β_2-agonist and steroid. Since the use of formoterol instead of salmoterol gives a much more rapid onset the combinations according to the invention have a number of advantages compared to the combinations disclosed i EP 416950 and EP 41651. The combination according to present invention permits a twice daily dosing regime as a basic treatment of asthma, particularly nocturnal asthma.

The present invention provides a medicament containing, separately, or together, (i) formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and (ii) budesonide for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

The invention also provides a pharmaceutical composition for administration by inhalation in the treatment of respiratory disorders which composition comprises formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

According to another aspect of the invention there are provided pharmaceutical compositions comprising effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide as a combined preparation for simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

The invention further provides formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide for use in combination therapy by simultaneous, sequential or separate administration by inhalation in the treatment of respiratory disorders.

Further the invention provides the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorders and the use of budesonide in the manufacture of a medicament for combination therapy where formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide are administered simultaneously, sequentially or separately by inhalation in the treatment of respiratory disorders.

The invention additionally relates to the use of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide in the manufacture of a medicament for combination therapy for simultaneous, sequential or separate administration of formoterol and budesonide by inhalation in the treatment of respiratory disorders.

According to a further feature of the invention there is provided a method of treating respiratory disorders which comprises the simultaneous, sequential or separate administration by inhalation of effective amounts of formoterol (and/or a physiologically acceptable salt and/or solvate thereof) and budesonide.

Suitable physiologically salts of formoterol include acid addition salts derived from inorganic and organic acids, such as the hydrochloride, hydrobromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, 4-methoxybenzoate, 2- or 4-hydroxybenzoate, 4-chlorobenzoate, p-toluenesulphonate, methanesulphonate, ascorbate, salicylate, acetate succinate, lactate, glutarate, gluconate, tricarballylate, hydroxynaphthalenecarboxylate or oleate. Formoterol is preferably used in the form of its fumarate salt and as a dihydrate.

The ratio of formoterol to budesonide used according to the invention is preferably within the range of 1:4 to 1:70. The two drugs may be administered separately in the same ratio.

The intended dose regimen is a twice daily administration, where the suitable daily dose of formoterol is in the range of 6 to 100 μg with a preferred dose of 6–48 μg and the suitable daily dose for budesonide is 50 to 4800 μg with a preferred dose of 100–1600 μg. The particular dose used will strongly depend on the patient (age, weight etc) and the severity of the disease (mild, moderate, severe asthma etc).

For administration, the combination is suitably inhaled from a nebulizer, from a pressurized metered dose inhaler or as a dry powder from a dry powder inhaler (e.g. as sold under the trade mark Turbuhaler) or from a dry powder inhaler utilizing gelatin, plastic or other capsules, cartridges or blister packs.

A diluent or carrier, generally non-toxic and chemically inert to the medicament e.g. lactose, dextran, mannitol or glucose or any additives that will give the medicament a desired taste, can be added to the powdered medicament.

Examples of the preparation of suitable dosage forms according to the invention include the following: Formoterol fumarate dihydrate and budesonide (optionally premicronized) are mixed in the proportions given above. The agglomerated, free-flowing micronized mixture may be filled into a dry powder inhaler such as sold under the trade mark Turbuhaler. When a capsule system is used, it is desirable to include a filler in the mixture.

The micronized mixture may be suspended or dissolved in a liquid propellant mixture which is kept in a container that is sealed with a metering valve and fitted into a plastic actuator. The propellants used may be chlorofluorocarbons of different chemical formulae. The most frequently used chlorofluorocarbon propellants are trichloromonofluoromethane (propellant 11), dichlorodifluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 114), tetrafluoroethane (propellant 134a) and 1.1-difluoroethane (propellant 152a). Low concentrations of a surfactant such as sorbitan trioleate, lecithin, disodium dioctylsulphosuccinate or oleic acid may also be used to improve the physical stability.

The invention is further illustrated by way of example with reference to the following Examples.

EXAMPLE 1

Dry Powder Inhaler (Turbuhaler)

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 μg
Budesonide	200 μg

The storage unit of the inhaler is filled with sufficient material for at least 200 doses.

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	24 μg
Budesonide	200 μg

The storage unit is filled with sufficient material for at least 200 doses.

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 μg
Budesonide	100 μg

The storage unit is filled with sufficient material for at least 200 doses.

EXAMPLE 2

Metered Dose Inhaler

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 μg
Budesonide	200 μg
Stabilizer	0.1–0.7 mg
Propellant	25–100 μl
Formoterol (as fumarate dihydrate)	24 μg
Budesonide	200 μg
Stabilizer	0.1–0.7 mg
Propellant	25–100 μl
Formoterol (as fumarate dihydrate)	12 μg
Budesonide	200 μg
Stabilizer	0.1–0.7 mg
Propellant	25–100 μl

EXAMPLE 3

Metered Dose Dry Powder Formulation

Active ingredient	Per dose
Formoterol (as fumarate dihydrate)	12 μg
Budesonide	200 μg
Lactose	up to 5, 12.5 or 25 mg
Formoterol (as fumarate dihydrate)	24 μg
Budesonide	200 μg
Lactose	up to 5, 12.5 or 25 mg
Formoterol (as fumarate dihydrate)	12 μg
Budesonide	100 μg
Lactose	up to 5, 12.5 or 25 mg

We claim:

1. A medicament containing as active ingredients effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:4 to 1:60.

2. The medicament of claim 1 wherein the active ingredients are in dry powder form.

3. The medicament of claim 1 or 2 wherein the formoterol is in the form of the fumarate dihydrate.

4. A pharmaceutical composition which comprises effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:4 to 1:60, together with a pharmaceutically acceptable carrier.

5. The pharmaceutical composition of claim 4 wherein the formoterol is in the form of the fumarate dihydrate.

6. A pharmaceutical composition according to claim 4 wherein the pharmaceutically acceptable carrier is lactose.

7. A pharmaceutical composition according to claim 6 in dosage unit form.

8. A pharmaceutical composition according to claim 7 comprising 12 μg formoterol fumarate dihydrate, 200 μg budesonide and up to 25 mg lactose.

9. A medicament containing as active ingredients effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:1 to 1:60.

10. The medicament of claim 9 wherein the active ingredients are in dry powder form.

11. The medicament of claim 9 or 10 wherein the formoterol is in the form of the fumarate dihydrate.

12. A pharmaceutical composition which comprises effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:1 to 1:60, together with a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12 wherein the formoterol is in the form of the fumarate dihydrate.

14. A pharmaceutical composition according to claim 12 wherein the pharmaceutically acceptable carrier is lactose.

15. A pharmaceutical composition according to claim 14 in dosage unit form.

16. A pharmaceutical composition according to claim 15 comprising 12 μg formoterol fumarate dihydrate, 200 μg budesonide and up to 25 mg lactose.

17. A method for the treatment of asthma and other inflammatory respiratory disorders which comprises administering by inhalation to a host in need of such treatment effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:4 to 1:60.

18. The method according to claim 17, wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6–100 μg per day, and the effective amount of budesonide is 50–4800 μg per day.

19. The method according to claim 18 wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6–48 μg per day, and the effective amount of budesonide is 100–1600 μg per day.

20. The method according to any one of claims 17, 18 and 19 wherein the administration is performed from a dry powder inhaler.

21. The method according to claim 20 wherein the inhaler is a Turbuhaler™.

22. The method according to any one of claims 17, 18 and 19 wherein the administration is performed from a metered dose inhaler.

23. The method according to any one of claims 17, 18 and 19 wherein the formoterol is in the form of the fumarate dihydrate.

24. The method according to any one of claims 17, 18 and 19 wherein the administration is performed with a nebulizer.

25. A method according to any one of claims 17, 18 and 19 wherein the formoterol component and the budesonide component are administered simultaneously.

26. The method according to any one of claims 17, 18 and 19, wherein the physiologically acceptable salt of formoterol or the solvate thereof is administered in admixture with the budesonide.

27. A method for the treatment of asthma and other inflammatory respiratory disorders which comprises administering by inhalation to a host in need of such treatment effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:1 to 1:60.

28. The method according to claim 27, wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6–100 μg per day, and the effective amount of budesonide is 50–4800 μg per day.

29. The method according to claim 28 wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6–48 μg per day, and the effective amount of budesonide is 100–1600 μg per day.

30. The method according to any one of claims 27, 28 and 29 wherein the administration is performed from a dry powder inhaler.

31. The method according to claim 30 wherein the inhaler is a Turbuhaler™.

32. The method according to any one of claims 27, 28 and 29 wherein the administration is performed from a metered dose inhaler.

33. The method according to any one of claims 27, 28 and 29 wherein the formoterol is in the form of the fumarate dihydrate.

34. The method according to any one of claims 27, 28 and 29 wherein the administration is performed with a nebulizer.

35. The method according to any one of claims 27, 28 and 29 wherein the formoterol component and the budesonide component are administered simultaneously.

36. The method according to any one of claims 27, 28 and 29, wherein the physiologically acceptable salt of formoterol or the solvate thereof is administered in admixture with the budesonide.

* * * * *

XXXXXX-XX

SYMBICORT 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol*

SYMBICORT 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol*

*3.7 mcg formoterol as the free base, equivalent to 4.5 mcg formoterol fumarate dihydrate

For Oral Inhalation Only

Rx only

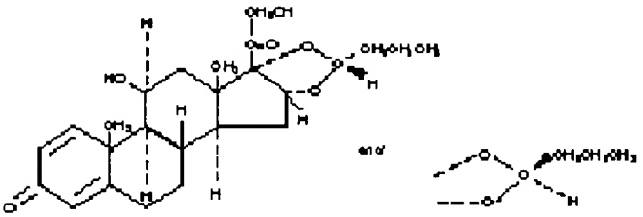
WARNING

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. Data from a large placebo-controlled US study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol may apply to formoterol (a long-acting beta$_2$-adrenergic agonist), one of the active ingredients in SYMBICORT (see WARNINGS).

DESCRIPTION

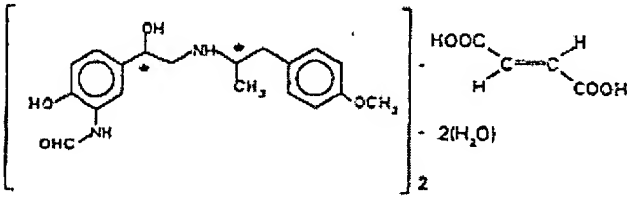
SYMBICORT 80/4.5 and SYMBICORT 160/4.5 each contain micronized budesonide and micronized formoterol fumarate dihydrate for oral inhalation only.

One active component of SYMBICORT is budesonide, a corticosteroid designated chemically as (RS)-11β, 16α, 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6 x 10^3.

The other active component of SYMBICORT is formoterol fumarate dihydrate, a selective beta$_2$-agonist designated chemically as (R*,R*)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl]formamide, (E)-2-butendioate(2:1), dihydrate. The empirical formula of formoterol is $C_{42}H_{56}N_4O_{14}$ and its molecular weight is 840.9. Its structural formula is:



Formoterol fumarate dihydrate is a powder which is slightly soluble in water. Its octanol-water partition coefficient at pH 7.4 is 2.6. The pKa of formoterol fumarate dihydrate at 25°C is 7.9 for the phenolic group and 9.2 for the amino group.

Each 10.2 g SYMBICORT 80/4.5 and SYMBICORT 160/4.5 canister is formulated as a hydrofluoroalkane (HFA 227; 1,1,1,2,3,3,3-heptafluoropropane)-propelled pressurized metered dose inhaler containing 120 actuations. After priming, each actuation meters either 91/5.1 mcg or 181/5.1 mcg from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg (budesonide micronized/formoterol fumarate dihydrate micronized) from the actuator. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between actuation of the device and inspiration through the delivery system. SYMBICORT also contains povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant.

SYMBICORT should be primed before using for the first time by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well for 5 seconds before each spray and releasing 2 test sprays into the air away from the face.

CLINICAL PHARMACOLOGY

Mechanism of Action

SYMBICORT

SYMBICORT contains both budesonide and formoterol; therefore, the mechanisms of action described below for the individual components apply to SYMBICORT. These drugs represent two classes of medications (a synthetic corticosteroid and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical, physiological, and inflammatory indices of asthma.

Budesonide

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

In glucocorticoid receptor affinity studies, the 22R form of budesonide was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses of budesonide. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites.

Formoterol:

Formoterol fumarate is a long-acting selective $beta_2$-adrenergic agonist ($beta_2$-agonist) with a rapid onset of action. Inhaled formoterol fumarate acts locally in the lung as a bronchodilator. *In vitro* studies have shown that formoterol has more than 200-fold greater agonist activity at $beta_2$-receptors than at $beta_1$-receptors. The *in vitro* binding selectivity to $beta_2$- over $beta_1$-adrenoceptors is higher for formoterol than for albuterol (5 times), whereas salmeterol has a higher (3 times) $beta_2$-selectivity ratio than formoterol.

Although $beta_2$-receptors are the predominant adrenergic receptors in bronchial smooth muscle and $beta_1$-receptors are the predominant receptors in the heart, there are also $beta_2$-receptors in the human heart comprising 10%-50% of the total beta-adrenergic receptors. The precise function of these receptors has not been established, but they raise the possibility that even highly selective $beta_2$-agonists may have cardiac effects.

The pharmacologic effects of $beta_2$-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

In vitro tests show that formoterol is an inhibitor of the release of mast cell mediators, such as histamine and leukotrienes, from the human lung. Formoterol also inhibits histamine-induced plasma albumin extravasation in anesthetized guinea pigs and inhibits allergen-induced eosinophil influx in dogs with airway hyper-responsiveness. The relevance of these in vitro and animal findings to humans is unknown.

Animal Pharmacology

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical significance of these findings is unknown.

Pharmacokinetics

Symbicort

In a single-dose study, higher than recommended doses of SYMBICORT (12 inhalations of SYMBICORT 160/4.5 mcg) were administered to patients with moderate asthma. Peak plasma concentrations for budesonide of 4.5 nmol/L occurred at 20 minutes following dosing and peak concentrations for formoterol of 136 pmol occurred at 10 minutes following dosing. Approximately 8% of the delivered dose of formoterol was recovered in the urine as unchanged drug. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler (DPI) at the same delivered dose. Following administration of SYMBICORT, the half-life of the budesonide component was 4.7 hours and for the formoterol component was 7.9 hours.

In a repeat dose study, the highest recommended dose of SYMBICORT (160/4.5 mcg, 2 inhalations twice daily) was administered to patients with moderate asthma and healthy subjects for one week. Peak plasma concentrations of budesonide (1.2 nmol/L) and formoterol (28 pmol/L) occurred at 21 and 10 minutes, respectively, in asthma patients. Peak plasma concentrations for budesonide and formoterol were about 30 to 40% higher in healthy subjects to that in asthma patients. However, the total systemic exposure was comparable to that in asthma patients.

Following administration of SYMBICORT (160/4.5 mcg, two or four inhalations twice daily) for five days in healthy subjects, plasma concentrations of budesonide and formoterol generally increased in proportion to dose. Additionally in this study, the accumulation index for the two inhalation groups was 1.32 for budesonide and 1.77 for formoterol.

Special Populations

Geriatric

The pharmacokinetics of SYMBICORT in geriatric patients have not been specifically studied.

Pediatric

Plasma concentrations of budesonide were measured following administration of 4 inhalations of SYMBICORT 160/4.5 mcg in a single dose study in pediatric patients with asthma, 6-11 years of age. Urine was collected for determination of formoterol excretion. Peak budesonide concentrations of 1.4 nmol/L occurred at 20 minutes post-dose. Approximately 3.5% of the delivered formoterol dose was recovered in the urine as unchanged formoterol. This study also demonstrated that the total systemic exposure to budesonide from SYMBICORT was approximately 30% lower than from inhaled budesonide via a dry powder inhaler which was also evaluated at the same delivered dose.

Gender/Race

Specific studies to examine the effects of gender and race on the pharmacokinetics of SYMBICORT have not been conducted. Population PK analysis of the SYMBICORT data indicates that gender does not affect the pharmacokinetics of budesonide and formoterol. No conclusions can be drawn on the effect of race due to the low number of non-Caucasians evaluated for PK.

Renal or Hepatic Insufficiency

There are no data regarding the specific use of SYMBICORT in patients with hepatic or renal impairment. Reduced liver function may affect the elimination of corticosteroids. Budesonide pharmacokinetics was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous budesonide pharmacokinetics was, however, similar in cirrhotic patients and in healthy subjects. Specific data with formoterol is not available, but since formoterol is primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver impairment.

Drug-Drug Interactions

A single dose crossover study was conducted to compare the pharmacokinetics of eight inhalations of the following: budesonide, formoterol, and budesonide plus formoterol administered concurrently. The results of the study indicated that there was no evidence of a pharmacokinetic interaction between the two components of SYMBICORT.

Ketoconazole, a potent inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide. Specific drug-drug interaction studies with formoterol have not been performed.

Budesonide

Absorption

Orally inhaled budesonide is rapidly absorbed in the lungs and peak concentration is typically reached within 20 minutes. After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6-13%, due to extensive first pass metabolism. In contrast, most of the budesonide delivered to the lungs was systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lung (as assessed by plasma concentration method and using a budesonide containing dry-powder inhaler) with an absolute systemic availability of 39% of the metered dose. Peak steady-state plasma concentrations of budesonide administered by DPI in adults with asthma averaged 0.6 and 1.6 nmol/L at doses of 180 mcg and 360 mcg twice daily, respectively.

In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing of inhaled budesonide.

Distribution

The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended inhaled doses. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

In vitro studies with human liver homogenates have shown that budesonide was rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites was less than 1% of that of the parent compound. No qualitative differences between the in vitro and in vivo metabolic patterns were detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination

Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine. The 22R form of budesonide was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose.

Formoterol

Absorption

Inhaled formoterol is rapidly absorbed; peak plasma concentrations are typically reached at the first plasma sampling time, within 5-10 minutes after dosing. As with many drug products for oral inhalation, it is likely that the majority of the inhaled formoterol delivered is swallowed and then absorbed from the gastrointestinal tract.

Distribution

Over the concentration range of 10-500 nmol/L, plasma protein binding for the RR and SS enantiomers of formoterol was 46 and 58%, respectively. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

Metabolism and Excretion

The metabolism and excretion of formoterol were studied in 4 healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces. The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6 and CYP2C have been identified as being primarily responsible for O-demethylation.

Pharmacodynamics

Symbicort

In a single-dose cross-over study involving 201 patients with persistent asthma, single-dose treatments of 4.5, 9, and 18 mcg of formoterol in combination with 320 mcg of budesonide delivered via SYMBICORT were compared to budesonide 320 mcg alone. Dose-ordered improvements in FEV_1 were demonstrated when compared with budesonide. ECGs and blood samples for glucose and potassium were obtained post dose. For SYMBICORT, small mean increases in serum glucose and decreases in serum potassium (+0.44 mmol/L and -0.18 mmol/L at the highest dose, respectively) were observed with increasing doses of formoterol, compared to budesonide. In ECGs, SYMBICORT produced small dose-related mean increases in heart rate (approximately 3 bpm at the highest dose), and QTc intervals (3-6 msec) compared to budesonide alone. No subject had a QT or QTc value $\geq$500 msec.

In the United States, five 12-week, active- and placebo- controlled studies evaluated 2152 patients aged 12 and older with asthma. Systemic pharmacodynamic effects of formoterol (heart/pulse rate, blood pressure, QTc interval, potassium, and glucose) were similar in patients treated with SYMBICORT compared with patients treated with formoterol dry inhalation powder 4.5 mcg, 2 inhalations twice daily. No patient had a QT or QTc value $\geq$500 msec during treatment.

In 3 placebo-controlled studies in adolescents and adults with asthma aged 12 and older, a total of 1232 patients (553 patients in the SYMBICORT group) had evaluable continuous 24-hour electrocardiographic monitoring. Overall, there were no important differences in the occurrence of ventricular or supraventricular ectopy and no evidence of increased risk for clinically significant dysrhythmia in the SYMBICORT group compared to placebo.

Overall, no clinically important effects on HPA axis, as measured by 24-hour urinary cortisol, were observed for SYMBICORT-treated adult or adolescent patients at doses up to 640/18 mcg/day compared to budesonide.

Budesonide

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Inhaled budesonide has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in patients with hyperreactive airways. The clinical relevance of these models is not certain.

Pretreatment with inhaled budesonide, 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The systemic effects of inhaled corticosteroids are related to the systemic exposure to such drugs. Pharmacokinetic studies have demonstrated that in both adults and children with asthma the systemic exposure to budesonide is lower with SYMBICORT compared with inhaled budesonide administered at the same delivered dose via a dry powder inhaler (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, SYMBICORT**). Therefore, the systemic effects (HPA axis and growth) of budesonide delivered from SYMBICORT would be expected to be no greater than what is reported for inhaled budesonide when administered at comparable doses via the dry powder inhaler (see **PRECAUTIONS, Pediatric Use**).

The effects of inhaled budesonide administered via a dry powder inhaler on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with budesonide treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 mcg of inhaled budesonide twice daily for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10 mg prednisone resulted in a 35% reduction. In this study, no patient on budesonide at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of budesonide when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of budesonide in recommended doses was associated with higher stimulated cortisol response compared to baseline following 1 year of therapy.

Formoterol

While the pharmacodynamic effect is via stimulation of beta-adrenergic receptors; excessive activation of these receptors commonly leads to skeletal muscle tremor and cramps, insomnia, tachycardia, decreases in plasma potassium, and increases in plasma glucose. Inhaled formoterol, like other beta-adrenergic agonist drugs, can produce dose-related cardiovascular effects and effects on blood glucose and/or serum potassium (see **PRECAUTIONS, General**). For Symbicort, these effects are detailed in the **CLINICAL PHARMACOLOGY, Pharmacodynamics, SYMBICORT** section.

Use of long-acting $beta_2$-adrenergic agonist drugs can result in tolerance to bronchoprotective and bronchodilatory effects.

Rebound bronchial hyper-responsiveness after cessation of chronic long-acting beta-agonists therapy has not been observed.

Clinical Studies

SYMBICORT has been studied in patients with asthma 12 years of age and older. In two clinical studies comparing SYMBICORT with the individual components, improvements in most efficacy endpoints were greater with SYMBICORT than with the use of either budesonide or formoterol alone. In addition, one clinical study showed similar results between SYMBICORT and the concurrent use of budesonide and formoterol at corresponding doses from separate inhalers.

The safety and efficacy of SYMBICORT were demonstrated in two randomized, double-blind, placebo-controlled US clinical studies involving 1076 patients 12 years of age and older. Fixed SYMBICORT dosages of 160/9 mcg, and 320/9 mcg twice daily (each dose administered as 2 inhalations of the 80/4.5- and 160/4.5-mcg strengths, respectively) were compared with the monocomponents (budesonide and formoterol) and placebo to provide information about appropriate dosing to cover a range of asthma severity.

Study 1: Clinical Study with SYMBICORT 160/4.5: This 12-week study evaluated 596 patients 12 years of age and older by comparing: SYMBICORT 160/4.5 mcg, the free combination of budesonide 160 mcg plus formoterol 4.5 mcg in separate inhalers, budesonide 160 mcg, formoterol 4.5 mcg, and placebo; each administered as 2 inhalations twice daily. The study included a 2-week run-in period with budesonide 80 mcg, 2 inhalations twice daily. Most patients had moderate to severe asthma and were using moderate to high doses of inhaled corticosteroids prior to study entry. Randomization was stratified by previous inhaled corticosteroid treatment (71.6% on moderate- and 28.4% on high-dose inhaled corticosteroid). Mean percent predicted FEV_1 at baseline was 68.1% and was similar across treatment groups. The co-primary efficacy endpoints were 12-hour-average post-dose FEV_1 at week 2, and pre-dose FEV_1 averaged over the course of the study. The study also required that patients who satisfied a pre-defined asthma worsening criterion to be withdrawn. The pre-defined asthma worsening criteria were: a clinically important decrease in FEV_1 or peak expiratory flow (PEF), increase in rescue albuterol use, nighttime awakening due to asthma, emergency intervention or hospitalization due to asthma, or requirement for asthma medication not allowed by the protocol. For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the

study at the discretion of the investigator if none of the other asthma worsening criteria were met. The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 1.

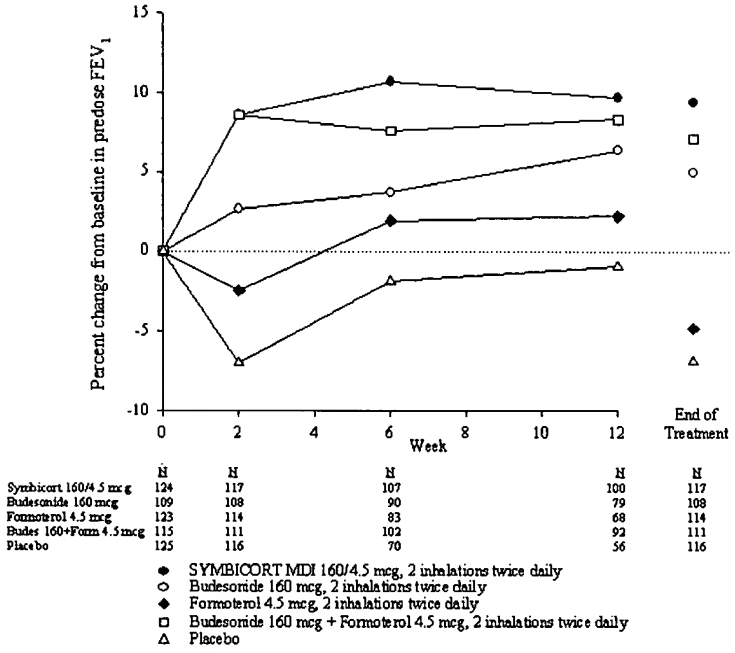
Table 1 – The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 1)

	SYMBICORT 160/4.5 (N=124)	**Budesonide 160 mcg plus Formoterol 4.5 mcg (N=115)**	**Budesonide 160 mcg (N=109)**	**Formoterol 4.5 mcg (N=123)**	**Placebo (N=125)**
Patients withdrawn due to predefined asthma event*	13 (10.5)	13 (11.3)	22 (20.2)	44 (35.8)	62 (49.6)
Patients with a predefined asthma event*†	37 (29.8)	24 (20.9)	48 (44.0)	68 (55.3)	84 (67.2)
Decrease in FEV_1	4 (3.2)	8 (7.0)	7 (6.4)	15 (12.2)	14 (11.2)
Rescue medication use	2 (1.6)	0	3 (2.8)	3 (2.4)	7 (5.6)
Decrease in AM PEF	2 (1.6)	5 (4.3)	5 (4.6)	17 (13.8)	15 (12.0)
Nighttime awakening‡	24 (19.4)	11 (9.6)	29 (26.6)	32 (26.0)	49 (39.2)
Clinical exacerbation	7 (5.6)	6 (5.2)	5 (4.6)	17 (13.8)	16 (12.8)

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1 which was assessed at each clinic visit.
†Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.
‡For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in FEV_1 measured immediately prior to dosing (predose) over 12 weeks is displayed in Figure 1. Because this study used predefined withdrawal criteria for worsening asthma, which caused a differential withdrawal rate in the treatment groups, predose FEV_1 results at the last available study visit (end of treatment, EOT) are also provided. Patients receiving SYMBICORT 160/4.5 mcg had significantly greater mean improvements from baseline in predose FEV_1 at the end of treatment (0.19 L, 9.4%) compared with budesonide 160 mcg (0.10 L, 4.9%), formoterol 4.5 mcg (-0.12 L, -4.8%), and placebo (-0.17 L, -6.9%).

Figure 1 - Mean Percent Change From Baseline in predose FEV_1 Over 12 Weeks (Study 1)



	N	N	N	N	N
Symbicort 160/4.5 mcg	124	117	107	100	117
Budesonide 160 mcg	109	108	90	79	108
Formoterol 4.5 mcg	123	114	83	68	114
Budes 160+Form 4.5 mcg	115	111	102	92	111
Placebo	125	116	70	56	116

● SYMBICORT MDI 160/4.5 mcg, 2 inhalations twice daily
○ Budesonide 160 mcg, 2 inhalations twice daily
◆ Formoterol 4.5 mcg, 2 inhalations twice daily
□ Budesonide 160 mcg + Formoterol 4.5 mcg, 2 inhalations twice daily
△ Placebo

The effect of SYMBICORT 160/4.5 mcg 2 inhalations twice daily on selected secondary efficacy variables, including morning and evening PEF, albuterol rescue use, and asthma symptoms over 24 hours on a 0-3 scale is shown in Table 2.

Table 2 - Mean values for selected secondary efficacy variables (Study 1)

Efficacy Variable	SYMBICORT 160/4.5 (N*=124)	Budesonide 160 mcg + Formoterol 4.5 mcg (N*=115)	Budesonide 160 mcg (N*=109)	Formoterol 4.5 mcg (N*=123)	Placebo (N*=125)
AM PEF (L/min)					
Baseline	341	338	342	339	355
Change from Baseline	35	28	9	–9	–18
PM PEF (L/min)					
Baseline	351	348	357	354	369
Change from Baseline	34	26	7	–7	–18
Albuterol rescue use					
Baseline	2.1	2.3	2.7	2.5	2.4
Change from Baseline	–1.0	–1.5	–0.8	–0.3	0.8
Average symptom score/day (0-3 scale)					
Baseline	0.99	1.03	1.04	1.04	1.08
Change from Baseline	–0.28	–0.32	–0.14	–0.05	0.10

*Number of patients (N) varies slightly due to the number of patients for whom data were available for each variable. Results shown are based on last available data for each variable.

The subjective impact of asthma on patients' health-related quality of life was evaluated through the use of the standardized Asthma Quality of Life Questionnaire (AQLQ(S)) (based on a 7-point scale where 1 = maximum impairment and 7 = no impairment). Patients receiving SYMBICORT 160/4.5 had clinically meaningful improvement in overall asthma-specific quality of life, as defined by a mean difference between treatment groups of >0.5 points in change from baseline in overall AQLQ score (difference in AQLQ score of 0.70 [95% CI 0.47, 0.93] compared to placebo).

Study 2: Clinical Study with SYMBICORT 80/4.5

This 12-week study was similar in design to Study 1, and included 480 patients 12 years of age and older. This study compared: SYMBICORT 80/4.5 mcg, budesonide 80 mcg, formoterol 4.5 mcg, and placebo; each administered as 2 inhalations twice-daily. The study included a 2-week

placebo run-in period. Most patients had mild to moderate asthma and were using low to moderate doses of inhaled corticosteroids prior to study entry. Mean percent predicted FEV_1 at baseline was 71.3% and was similar across treatment groups. Efficacy variables and endpoints were identical to those in Study 1.

The percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma is shown in Table 3. The method of assessment and criteria used were identical to that in Study 1.

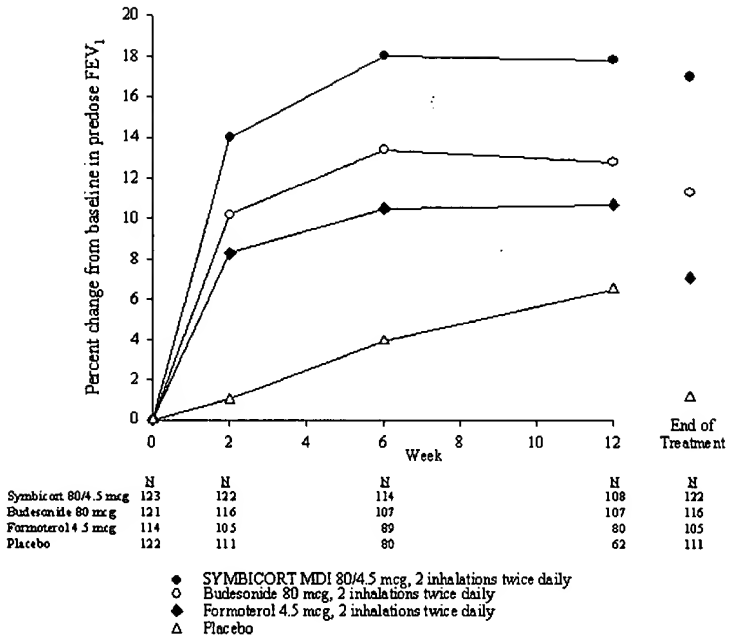
Table 3 - The number and percentage of patients withdrawing due to or meeting predefined criteria for worsening asthma (Study 2)

	SYMBICORT 80/4.5 (N=123)	**Budesonide 80 mcg (N=121)**	**Formoterol 4.5 mcg (N=114)**	**Placebo (N=122)**
Patients withdrawn due to predefined asthma event*	9 (7.3)	8 (6.6)	21 (18.4)	40 (32.8)
Patients with a predefined asthma event*†	23 (18.7)	26 (21.5)	48 (42.1)	69 (56.6)
Decrease in FEV_1	3 (2.4)	3 (2.5)	11 (9.6)	9 (7.4)
Rescue medication use	1 (0.8)	3 (2.5)	1 (0.9)	3 (2.5)
Decrease in AM PEF	3 (2.4)	1 (0.8)	8 (7.0)	14 (11.5)
Nighttime awakening‡	17 (13.8)	20 (16.5)	31 (27.2)	52 (42.6)
Clinical exacerbation	1 (0.8)	3 (2.5)	5 (4.4)	20 (16.4)

*These criteria were assessed on a daily basis irrespective of the timing of the clinic visit, with the exception of FEV_1 which was assessed at each clinic visit.
†Individual criteria are shown for patients meeting any predefined asthma event, regardless of withdrawal status.
‡For the criterion of nighttime awakening due to asthma, patients were allowed to remain in the study at the discretion of the investigator if none of the other criteria were met.

Mean percent change from baseline in predose FEV_1 over 12 weeks is displayed in Figure 2.

Figure 2 - Mean percent change from baseline in predose FEV_1 over 12 weeks (Study 2)



Efficacy results for other secondary endpoints, including quality of life, were similar to those observed in Study 1.

Onset and Duration of Action and Progression of Improvement in Asthma Control
The onset of action and progression of improvement in asthma control were evaluated in the 2 pivotal clinical studies. The median time to onset of clinically significant bronchodilation (>15% improvement in FEV_1) was seen within 15 minutes. Maximum improvement in FEV_1 occurred within 3 hours, and clinically significant improvement was maintained over 12 hours. Figures 3 and 4 show the percent change from baseline in postdose FEV_1 over 12 hours on the day of randomization and on the last day of treatment for Study 1.

Reduction in asthma symptoms and in albuterol rescue use, as well as improvement in morning and evening PEF, occurred within 1 day of the first dose of SYMBICORT; improvement in these variables were maintained over the 12 weeks of therapy.

Following the initial dose of SYMBICORT, FEV_1 improved markedly during the first 2 weeks of treatment, continued to show improvement at the Week 6 assessment, and was maintained through Week 12 for both studies.

No diminution in the 12-hour bronchodilator effect was observed with either SYMBICORT 80/4.5 mcg or SYMBICORT 160/4.5 mcg as assessed by FEV_1 following 12 weeks of therapy or at the last available visit.

FEV_1 data from Study 1 evaluating SYMBICORT 160/4.5 mcg is displayed in Figures 3 and 4.

Figure 3 - Mean Percent Change From Baseline in FEV_1 on Day of Randomization (Study 1)

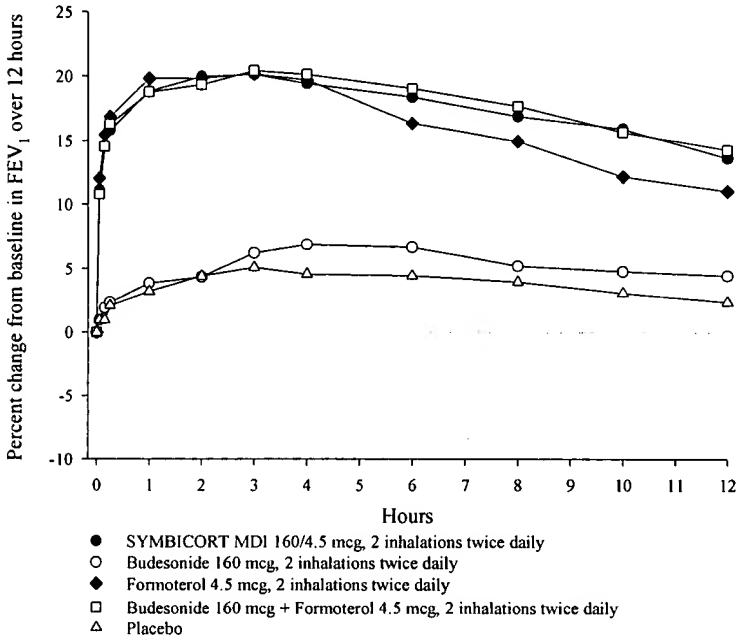
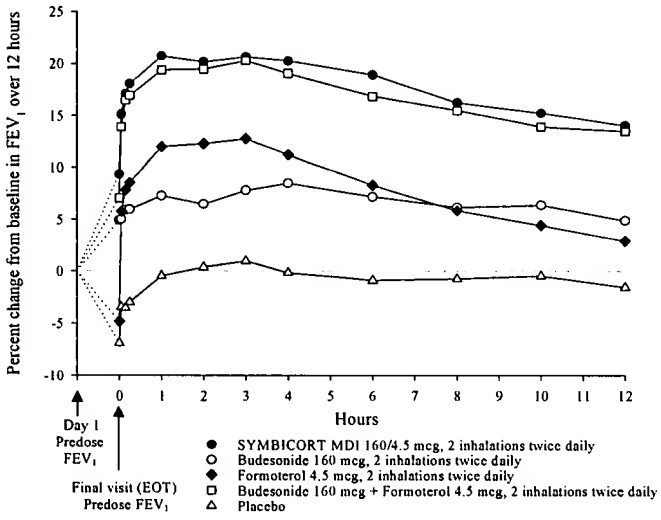


Figure 4 - Mean Percent Change From Baseline in FEV_1 At End of Treatment (Study 1)



INDICATIONS AND USAGE

SYMBICORT is indicated for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death (see WARNINGS). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated in patients whose asthma can be successfully managed by inhaled corticosteroids along with occasional use of inhaled, short-acting $beta_2$-agonists.

SYMBICORT is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

SYMBICORT is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to any of the ingredients in SYMBICORT contraindicates its use.

WARNINGS

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to-

medium dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

- A 28-week, placebo controlled US study comparing the safety of salmeterol with placebo, each added to usual asthma therapy, showed an increase in asthma-related deaths in patients receiving salmeterol (13/13,176 in patients treated with salmeterol vs 3/13,179 in patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). The increased risk of asthma-related death may represent a class effect of the long-acting $beta_2$-adrenergic agonists, including formoterol. No study adequate to determine whether the rate of asthma-related death is increased with SYMBICORT has been conducted.

- Clinical studies with formoterol suggested a higher incidence of serious asthma exacerbations in patients who received formoterol than in those who received placebo. The sizes of these studies were not adequate to precisely quantify the differences in serious asthma exacerbation rates between treatment groups.

SYMBICORT Should Not Be Initiated In Patients During Rapidly Deteriorating Or Potentially Life-Threatening Episodes Of Asthma.

Do Not Use SYMBICORT to Treat Acute Symptoms. SYMBICORT should not be used to treat acute symptoms of asthma. An inhaled, short-acting $beta_2$-agonist (e.g., albuterol), should be used to relieve acute asthma symptoms. Therefore, when prescribing SYMBICORT, the physician must also provide the patient with an inhaled, short-acting $beta_2$-agonist for treatment of symptoms that occur acutely, despite regular twice-daily (morning and evening) use of SYMBICORT.

When beginning treatment with SYMBICORT, patients who have been taking oral or inhaled, short-acting $beta_2$-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs. For patients on SYMBICORT, short-acting, inhaled $beta_2$-agonists should only be used for symptomatic relief of acute asthma symptoms (see **PRECAUTIONS, Information for Patients**).

Watch for Increasing Use of Inhaled, Short-Acting $Beta_2$-Agonists, Which Is a Marker of Deteriorating Asthma. Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient's inhaled, short-acting $beta_2$-agonist becomes less effective, the patient needs more inhalations than usual, or the patient develops a significant decrease in lung function, these may be markers of destabilization of asthma. In this setting, the patient requires immediate reevaluation and reassessment of the treatment regimen, giving special consideration to the possible need for replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating systemic corticosteroids. Patients should not use more than two actuations twice daily (morning and evening) of SYMBICORT.

SYMBICORT Should Not be Used For Transferring Patients from Systemic Corticosteroid Therapy. Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids. Deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months may be required for recovery of HPA function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although inhaled corticosteroid therapy may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Do Not Use an Inhaled, Long-Acting Beta$_2$-Agonist in Conjunction With SYMBICORT. Patients who are receiving SYMBICORT twice daily should not use additional formoterol or other long-acting inhaled beta$_2$-agonists (e.g., salmeterol) for prevention of exercise-induced bronchospasm (EIB) or the maintenance treatment of asthma. Additional benefit would not be gained from using supplemental formoterol or salmeterol for prevention of EIB since SYMBICORT already contains an inhaled, long-acting beta$_2$-agonist.

Do Not Exceed Recommended Dosage. SYMBICORT should not be used more often or at higher doses than recommended. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected. In addition, data from clinical studies with formoterol dry powder inhaler suggest that the use of doses higher than recommended (24 mcg twice daily) is associated with an increased risk of serious asthma exacerbations. In a 52-week active-controlled safety study evaluating SYMBICORT 160/4.5, patients treated with twice the highest recommended dose of SYMBICORT demonstrated a similar safety profile to that of patients treated with the highest recommended dose.

Paradoxical Bronchospasm. As with other inhaled asthma medications SYMBICORT, may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with SYMBICORT, treatment with SYMBICORT should be discontinued immediately and alternate therapy should be instituted.

Immediate Hypersensitivity Reactions. Immediate hypersensitivity reactions, such as urticaria, angioedema, rash, and bronchospasm may occur after administration of SYMBICORT.

Cardiovascular Disorders. SYMBICORT, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Formoterol, a component of SYMBICORT, may produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. Although such effects are uncommon after administration of SYMBICORT at recommended doses, if they occur, the drug may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical significance of these findings is unknown.

Discontinuation of Systemic Corticosteroids. Transfer of patients from systemic corticosteroid therapy to inhaled corticosteroids may unmask conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eczema, and arthritis.

Immunosuppression. Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in susceptible children or adults using corticosteroids. In such children or adults who have not had these diseases or been properly immunized, particular care should be taken to avoid exposure. It is unknown how the dose, route, and duration of corticosteroid administration affect the risk of developing a disseminated infection. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intramuscular immunoglobulin (IG), as appropriate may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered. The immune responsiveness to varicella vaccine was evaluated in pediatric patients with asthma ages 12 months to 8 years with budesonide inhalation suspension (see **PRECAUTIONS, Drug Interactions**).

PRECAUTIONS

General

Sympathomimetic Effects. The cardiovascular and central nervous system effects seen with all sympathomimetic drugs (e.g., increased blood pressure, heart rate, excitement) can occur after use of formoterol, a component of SYMBICORT, and may require discontinuation of SYMBICORT. SYMBICORT, like all medications containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension; in patients with convulsive disorders, untreated hypokalemia, or thyrotoxicosis; and in patients who are unusually responsive to sympathomimetic amines.

As has been described with other beta-adrenergic agonist bronchodilators, clinically important changes in electrocardiograms, systolic and/or diastolic blood pressure, and pulse rate were seen

infrequently in individual patients during controlled clinical studies with SYMBICORT at recommended doses.

Metabolic and Other Effects. Long-term use of orally inhaled corticosteroids, such as budesonide, a component of SYMBICORT, may affect normal bone metabolism resulting in a loss of bone mineral density. In patients with major risk factors for decreased bone mineral content, such as tobacco use, advanced age, sedentary lifestyle, poor nutrition, family history or osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), orally inhaled corticosteroids may pose an additional risk.

Doses of the related beta$_2$-adrenoceptor agonist albuterol, when administered intravenously, have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. High doses of beta-adrenergic agonist medications may produce significant hypokalemia in some patients, through intracellular shunting, which may have the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.

Clinically important changes in blood glucose and/or serum potassium were seen rarely during clinical studies with SYMBICORT at recommended doses.

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Budesonide, a component of SYMBICORT, will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active, patients should not exceed the recommended dosage of SYMBICORT. Individual patients should be titrated to the lowest effective dose in order to minimize HPA dysfunction. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing SYMBICORT.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with SYMBICORT should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, the total daily dose of SYMBICORT should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Budesonide, a component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Patients should be maintained on the lowest dose of SYMBICORT that effectively controls their asthma (see **PRECAUTIONS, Pediatric Use**).

The long-term effects resulting from chronic use of budesonide on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown. The local and systemic effects of SYMBICORT in humans have been studied for up to one year (see **ADVERSE REACTIONS, Long Term Safety**).

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT.

Lower respiratory tract infections, including pneumonia, have been reported following the inhaled administration of corticosteroids, including budesonide, a component of SYMBICORT. In the 3 placebo-controlled US clinical studies, the incidence of lower respiratory tract infections, including pneumonia, was low, with no consistent evidence of increased risk for SYMBICORT compared to placebo.

In clinical studies with SYMBICORT, localized infections with *Candida albicans* have occurred in the mouth and pharynx. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with SYMBICORT therapy, but at times the dose of SYMBICORT may need to be temporarily decreased or interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex.

Information for Patients

Patients should be instructed to read the accompanying Medication Guide with each new prescription and refill.

Patients being treated with SYMBICORT should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

It is important that patients understand how to use the SYMBICORT inhaler device appropriately and how SYMBICORT should be used in relation to other asthma medications they are taking.

1. **Patients should be informed that long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death.** Patients should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, such as budesonide, the other component of SYMBICORT, or other asthma-controller therapy modifies this risk.

2. Patients should be instructed that the correct dose of SYMBICORT is 2 puffs inhaled twice daily of the appropriate dosage strength, 80/4.5 or 160/4.5. They should take 2 puffs of SYMBICORT in the morning and 2 puffs in the evening every day. The maximum daily recommended dose is 640/18 mcg budesonide/formoterol (given as two inhalations of SYMBICORT 160/4.5 twice daily). Do not use more than twice daily or use a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT as this will result in a daily dose of formoterol in excess of the dose determined to be safe. **Patients should also be instructed not to take SYMBICORT more often or use more puffs than you have prescribed.** If they miss a dose, they should be instructed to take their next dose at the same time they normally do.
3. **SYMBICORT is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose.** Acute symptoms should be treated with an inhaled, short-acting $beta_2$-agonist such as albuterol (the physician should provide the patient with such medication and instruct the patient on how it should be used).
4. The physician should be notified immediately if any of the following situations occur, which may be a sign of seriously worsening asthma:
   - Decreasing effectiveness of inhaled, short-acting $beta_2$-agonists
   - Need for more inhalations than usual of inhaled, short-acting $beta_2$-agonists
   - Significant decrease in lung function as outlined by the physician
   - Marked change in symptoms
5. When patients are prescribed SYMBICORT, other inhaled drugs and asthma medications should be used only as directed by a physician.
6. Patients who are receiving SYMBICORT should not use formoterol or another long-acting inhaled $beta_2$-agonist for prevention of exercise-induced bronchospasm or maintenance treatment of asthma.
7. Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.
8. Patients should be cautioned regarding common adverse effects associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor, or nervousness.
9. Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.
10. Long-term use of inhaled corticosteroids, including budesonide, a component of SYMBICORT, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
11. If the patient is pregnant or nursing, they should contact their physician about the use of SYMBICORT.
12. Results of clinical trials indicate that in most patients, clinically significant improvement occurred within 15 minutes of beginning treatment with SYMBICORT. The maximum benefit may not be achieved for 2 weeks or longer after starting treatment. Individual patients may experience a variable time to onset and degree of symptom relief.
13. The bronchodilation from a dose (2 inhalations) of SYMBICORT has been shown to last up to 12 hours or longer. The recommended dosage should not be exceeded.
14. The following measures should be observed when using SYMBICORT:
    - Patients should not attempt to take the inhaler apart.

- SYMBICORT should be primed before using the first time and also when the inhaler has not been used for more than 7 days by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray.
- Patients should replace the mouthpiece cover after each use.
- To remove any excess medication, patients should rinse their mouth with water after each dose (do not swallow) to decrease the risk of the development of oral candidiasis.
- Patients should clean the inhaler every 7 days by wiping the mouthpiece with a dry cloth.
- Use SYMBICORT only with the actuator supplied with the product. Discard the inhaler after 120 sprays have been used by the patient.
- Store in a dry place at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP] and out of the reach of children.

Drug Interactions

In clinical studies, concurrent administration of SYMBICORT and other drugs, such as short-acting beta$_2$-agonists, intranasal corticosteroids, and antihistamines/decongestants has not resulted in an increased frequency of adverse events. No formal drug interaction studies have been performed with SYMBICORT.

Short-Acting Beta$_2$-Agonists: In three 12-week, placebo-controlled US clinical studies, the mean daily need for albuterol rescue use in 401 adult and adolescent patients using SYMBICORT twice daily was approximately 0.8 inhalations/day, and ranged from 0 to 14 inhalations/day. Approximately 2% (N= 8) of the SYMBICORT patients in these studies averaged 6 or more inhalations per day. No cardiac adverse events were reported in these patients.

Methylxanthines and leukotriene modifying agents: The concurrent use of intravenously or orally administered methylxanthines (e.g., aminophylline, theophylline) by patients receiving SYMBICORT has not been completely evaluated. In clinical trials with SYMBICORT, limited number of patients received concurrent methylxanthines or leukotriene modifying agents, and therefore no clinically meaningful conclusions on adverse events can be made.

Intranasal and systemic corticosteroids:
Among adult and adolescent patients participating in active- and placebo-controlled US clinical trials, twice daily SYMBICORT was used concurrently with intranasal budesonide in 105 patients and with any intranasal corticosteroids in 585 patients. Two hundred seventeen patients used courses of systemic corticosteroids while taking SYMBICORT. There were no important differences noted in the adverse event profiles between these groups.

Monoamine Oxidase Inhibitors and Tricyclic Antidepressants: SYMBICORT should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of formoterol, a component of SYMBICORT, on the vascular system may be potentiated by these agents. In clinical trials with SYMBICORT, a limited number of patients received tricyclic antidepressants and therefore no clinically meaningful conclusions on adverse events can be made.

Beta-Adrenergic Receptor Blocking Agents: Beta-blockers (including eye drops) may not only block the pulmonary effect of beta-agonists, such as formoterol, a component of SYMBICORT, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics: The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of SYMBICORT with nonpotassium-sparing diuretics.

Ketoconazole and Other Inhibitors of Cytochrome p450: The main route of metabolism of corticosteroids, including budesonide, a component of SYMBICORT, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (e.g., itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Caution should be exercised when considering the coadministration of SYMBICORT with long-term ketoconazole and other known potent CYP3A4 inhibitors.

Varicella Vaccine: An open-label non-randomized clinical study examined the immune responsiveness to varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or non-corticosteroid asthma therapy (n=92) (ie, $beta_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of $\geq$5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%) compared to patients treated with non-corticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chickenpox as a result of vaccination.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Budesonide

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant

increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (approximately equal to the maximum recommended human daily inhalation dose on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol

Long-term studies were conducted in mice using oral administration and rats using inhalation administration to evaluate the carcinogenic potential of formoterol fumarate.

In a 24-month carcinogenicity study in CD-1 mice, formoterol at oral doses of 0.1 mg/kg and above (approximately 20 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) caused a dose-related increase in the incidence of uterine leiomyomas.

In a 24-month carcinogenicity study in Sprague-Dawley rats, an increased incidence of mesovarian leiomyoma and uterine leiomyosarcoma were observed at the inhaled dose of 130 mcg/kg (approximately 60 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No tumors were seen at 22 mcg/kg (approximately 10 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Other beta-agonist drugs, have similarly demonstrated increases in leiomyomas of the genital tract in female rodents. The relevance of these findings to human use is unknown.

Formoterol was not mutagenic or clastogenic in Ames *Salmonella*/microsome plate test, mouse lymphoma test, chromosome aberration test in human lymphocytes, and rat micronucleus test.

A reduction in fertility and/or reproductive performance was identified in male rats treated with formoterol at an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In a separate study with male rats treated with an oral dose of 15 mg/kg (approximately 7000 times the maximum recommended human daily

inhalation dose on a mcg/m^2 basis), there were findings of testicular tubular atrophy and spermatic debris in the testes and oligospermia in the epididymides. No such effect was seen at 3 mg/kg (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No effect on fertility was detected in female rats at doses up to 15 mg/kg (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Pregnancy
Symbicort
Teratogenic Effects: Pregnancy Category C
SYMBICORT has been shown to be teratogenic and embryocidal in rats when given at inhalation doses of 12/0.66 mcg/kg (budesonide/formoterol) and above (less than the maximum recommended human daily inhaled dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed for fetuses at doses of 12/0.66 mcg/kg and above (less than the maximum recommended human daily inhaled dose on a mcg/m^2 basis). No teratogenic or embryocidal effects were detected at 2.5/0.14 mcg/kg (less than the maximum recommended human daily inhaled dose on a mcg/m^2 basis). There are no adequate and well-controlled studies in pregnant women. SYMBICORT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Budesonide
Teratogenic Effects:
As with other corticosteroids, budesonide has been shown to be teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 6 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg/day (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Formoterol

Teratogenic Effects:

Formoterol fumarate has been shown to be teratogenic, embryocidal, increase pup loss at birth and during lactation, and decreased pup weights in rats when given at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Umbilical hernia, a malformation, was observed in rat fetuses at oral doses of 3 mg/kg/day and above (approximately 1400 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Brachygnathia, a skeletal malformation, was observed for rat fetuses at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Pregnancy was prolonged at an oral dose of 15 mg/kg/day (approximately 7000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In another study in rats, no teratogenic effects were seen at inhalation doses up to 1.2 mg/kg/day (approximately 500 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol fumarate has been shown to be teratogenic in rabbits when given at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Subcapsular cysts on the liver were observed for rabbit fetuses at an oral dose of 60 mg/kg (approximately 54,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No teratogenic effects were observed at oral doses up to 3.5 mg/kg (approximately 3200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

There are no adequate and well-controlled studies with formoterol in pregnant women.

Nonteratogenic Effects
Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Use in Labor and Delivery
There are no well-controlled human studies that have investigated effects of SYMBICORT on preterm labor or labor at term. Because of the potential for beta-agonist interference with uterine contractility, use of SYMBICORT for management of asthma during labor should be restricted to those patients in whom the benefits clearly outweigh the risks.

Nursing Mothers
Since there are no data from controlled trials on the use of SYMBICORT by nursing mothers, a decision should be made whether to discontinue nursing or to discontinue SYMBICORT, taking into account the importance of SYMBICORT to the mother.

It is not known whether budesonide, one of the main components of SYMBICORT, is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

In reproductive studies in rats, formoterol was excreted in the milk. It is not known whether formoterol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if formoterol is administered to nursing women.

Pediatric Use
Safety and effectiveness of SYMBICORT in patients 12 years of age and older have been established in studies up to 12 months. In the two 12-week, double-blind, placebo-controlled US pivotal studies 25 patients 12 to 17 years of age were treated with SYMBICORT twice daily. Efficacy results in this age group were similar to those observed in patients 18 years and older. There were no obvious differences in the type or frequency of adverse events reported in this age group compared with patients 18 years of age and older.

The effectiveness of SYMBICORT in patients 6 to < 12 years of age has not been established.

Overall 1447 patients 6 to <12 years of age participated in placebo- and active-controlled SYMBICORT studies. Of these 1447 patients, 539 received SYMBICORT twice daily. The overall safety profile of these patients was similar to that observed in patients ≥12 years of age who also received SYMBICORT twice daily in studies of similar design.

Controlled clinical studies have shown that orally inhaled corticosteroids including budesonide, a component of SYMBICORT, may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of HPA axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The long-term effect of this reduction in growth velocity associated with orally inhaled corticosteroids, including the impact on final height are unknown. The potential for "catch-up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide DPI 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with budesonide DPI and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including SYMBICORT, should be monitored. If a child or adolescent on any corticosteroid appears to have growth suppression, the possibility that he/she is particularly sensitive to this effect should be considered. The potential growth effects of prolonged treatment should be weighed against the clinical benefits obtained. To minimize the systemic effects of orally inhaled corticosteroids, including SYMBICORT, each patient should be titrated to the lowest strength that effectively controls his/her asthma (see **DOSAGE AND ADMINISTRATION**).

Geriatric Use

In three 12-week, double-blind, placebo-controlled US clinical studies, 17 patients treated with SYMBICORT twice daily were 65 years of age or older, of whom 2 were 75 years of age or older. Of the total number of patients in clinical studies treated with SYMBICORT twice daily, 149 were 65 years of age or older, of whom, 25 were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients. As with other products containing beta$_2$-agonists, special caution should be observed when using SYMBICORT in geriatric patients who have concomitant cardiovascular disease that could be adversely affected by beta$_2$-agonists. Based on available data for SYMBICORT or its active components, no adjustment of dosage of SYMBICORT in geriatric patients is warranted.

ADVERSE REACTIONS

Long-acting beta$_2$-adrenergic agonists may increase the risk of asthma-related death (See **Boxed WARNING, WARNINGS, AND PRECAUTIONS** sections).

The incidence of common adverse events in the table below is based upon three 12-week, double-blind, placebo-controlled US clinical studies in which 401 adult and adolescent patients (148 males and 253 females) age 12 years and older were treated twice daily with 2 inhalations of SYMBICORT 80/4.5 or SYMBICORT 160/4.5, budesonide HFA metered dose inhaler (MDI) 80 or 160 mcg, formoterol dry powder inhaler (DPI) 4.5 mcg, or placebos (MDI and DPI).

Table 4 - Adverse Events (regardless of causality) Occurring at an Incidence of ≥3% and more Commonly than Placebo in any SYMBICORT Group

Treatment*	SYMBICORT		Budesonide HFA MDI		Formoterol DPI	Placebo MDI and DPI
Adverse Event	80/4.5 mcg N=277 (%)	160/4.5 mcg N=124 (%)	80 mcg N=121 (%)	160 mcg N=109 (%)	4.5 mcg N=237 (%)	N=400 (%)
Nasopharyngitis	10.5	9.7	14.0	11.0	10.1	9.0
Headache	6.5	11.3	11.6	12.8	8.9	6.5
Upper respiratory tract infection	7.6	10.5	8.3	9.2	7.6	7.8
Pharyngo-laryngeal pain	6.1	8.9	5.0	7.3	3.0	4.8
Sinusitis	5.8	4.8	5.8	2.8	6.3	4.8
Influenza	3.2	2.4	6.6	0.9	3.0	1.3
Back pain	3.2	1.6	2.5	5.5	2.1	0.8
Nasal congestion	2.5	3.2	2.5	3.7	1.3	1.0
Stomach discomfort	1.1	6.5	2.5	4.6	1.3	1.8
Vomiting	1.4	3.2	0.8	2.8	1.7	1.0
Oral candidiasis	1.4	3.2	0	0	0	0.8
Average Duration of Exposure (days)	77.7	73.8	77.0	71.4	62.4	55.9

*All treatments were administered as two inhalations twice daily.

The table above includes all events (whether or not considered drug-related by the investigators) that occurred at an incidence of ≥3% in any one SYMBICORT group and that were more common than in the placebo group with twice daily dosing. In considering these data, the increased average duration of exposure for SYMBICORT patients should be taken into account, as incidences are not adjusted for unequal treatment duration.

The following additional adverse events occurred in patients ≥12 years of age in the active and placebo-controlled clinical studies among 2344 patients treated with SYMBICORT twice daily with an incidence of ≥1% to <3% regardless of relationship to treatment, and are listed in decreasing order of incidence: asthma, nausea, dysphonia, pyrexia, sinus headache, diarrhea, pharyngitis, tremor, lower respiratory tract infection, muscle spasms, urinary tract infection, rhinitis, arthralgia, myalgia, dyspepsia, gastroenteritis viral, abdominal pain upper, dizziness, sinus congestion, rhinitis allergic, pain in extremity, palpitations, bronchitis acute, tension headache, migraine, post procedural pain. Additionally, the incidence of cough, bronchitis, and

viral upper respiratory tract infection was ≥3% (but each <4%) in this population but did not meet criteria for inclusion in the above table, as these data are not derived from placebo-controlled trials for subjects ≥12 years old.

The following adverse events occurred in this same population (patients ≥12 years of age) with an incidence <1%, and are listed because they have previously been reported during treatment with any formulation of inhaled SYMBICORT, budesonide and/or formoterol, regardless of the indication: immediate and delayed hypersensitivity reactions, e.g., rash, pruritus, urticaria, angioedema; cardiac events, e.g., tachycardia, coronary ischemia, atrial and ventricular tachyarrhythmias; variations in blood pressure, e.g., hypotension, hypertension, hypertensive crisis; hypokalemia; hyperglycemia; taste disturbance; psychiatric symptoms, e.g., irritability, anxiety, restlessness, nervousness, agitation, depression; skin bruising.

Long-Term Safety: Long-term safety studies in adolescent and adult patients 12 years of age and older, treated for up to one year at doses up to 1280/36 mcg/day (640/18 mcg twice daily), revealed neither clinically important changes in the incidence nor new types of adverse events emerging after longer periods of treatment. Similarly, no significant or unexpected patterns of abnormalities were observed for up to one year in safety measures including chemistry, hematology, ECG, Holter monitor, and HPA axis assessments.

Adverse Event Reports From Other Sources: Other relevant rare adverse events reported in the published literature, clinical trials or from worldwide marketing experience with any formulation of inhaled SYMBICORT, budesonide and/or formoterol, regardless of the indication include: immediate hypersensitivity reactions, such as anaphylactic reaction and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts, psychiatric symptoms, including aggressive reactions, behavioral disturbances, psychosis.

OVERDOSAGE

SYMBICORT: SYMBICORT contains both budesonide and formoterol; therefore, the risks associated with overdosage for the individual components described below apply to SYMBICORT. In pharmacokinetic studies, a total of 1920/54 mcg (12 actuations of SYMBICORT 160/4.5) was administered as a single dose to both healthy subjects and patients with asthma and was well tolerated. In a long-term active-controlled safety study, SYMBICORT 160/4.5 was well tolerated for up to 12 months at doses up to twice the highest recommended daily dose.

Clinical signs in dogs that received a single inhalation dose of SYMBICORT (a combination of budesonide and formoterol) in a dry powder included tremor, mucosal redness, nasal catarrh, redness of intact skin, abdominal respiration, vomiting, and salivation; in the rat, the only clinical sign observed was increased respiratory rate in the first hour after dosing. No deaths occurred in rats given a combination of budesonide and formoterol at acute inhalation dose of 97 and 3 mg/kg, respectively (approximately 1200 and 1350 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths occurred in dogs given a combination of budesonide and formoterol at the acute inhalation dose of 732 and 22 mcg/kg, respectively

(approximately 30 times the maximum recommended human daily inhalation dose of budesonide and formoterol on a mcg/m^2 basis).

Budesonide: The potential for acute toxic effects following overdose of budesonide is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see **PRECAUTIONS**). Budesonide at five times the highest recommended dose (3200 mcg daily) administered to humans for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

In mice the minimal inhalation lethal dose was 100 mg/kg (approximately 600 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats there were no deaths following the administration of an inhalation dose of 68 mg/kg (approximately 900 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). The minimal oral lethal dose in mice was 200 mg/kg (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis) and less than 100 mg/kg in rats (approximately 1300 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Formoterol: An overdose of formoterol would likely lead to an exaggeration of effects that are typical for $beta_2$-agonists; therefore, the following adverse experiences may occur: angina, hypertension or hypotension, palpitations, tachycardia, arrhythmia, prolonged QTc-interval, headache, tremor, nervousness, muscle cramps, dry mouth, insomnia, fatigue, malaise, seizures, metabolic acidosis, hypokalemia, hyperglycemia, nausea and vomiting. As with all sympathomimetic medications, cardiac arrest and even death may be associated with abuse of formoterol. Formoterol was well tolerated at a delivered dose of 90 mcg/day over 3 hours in adult patients with acute bronchoconstriction and when given three times daily for a total dose of 54 mcg/day for 3 days to stable asthmatics.

Treatment of formoterol overdosage consists of discontinuation of the medication together with institution of appropriate symptomatic and/or supportive therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of formoterol. Cardiac monitoring is recommended in cases of overdosage.

No deaths were seen in mice given formoterol at an inhalation dose of 276 mg/kg (more than 62,200 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). In rats the minimum lethal inhalation dose was 40 mg/kg (approximately 18,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). No deaths were seen in mice that received an oral dose of 2000 mg/kg (more than 450,000 times the maximum recommended human daily inhalation dose on a mcg/m^2 basis). Maximum non-lethal oral doses were 252 mg/kg in young rats and 1500 mg/kg in adult rats (approximately 114,000 times and 675,000 times the maximum recommended human inhalation dose on a mcg/m^2 basis).

DOSAGE AND ADMINISTRATION

SYMBICORT should be administered by the orally inhaled route in patients with asthma 12 years of age and older. SYMBICORT should not be used for transferring patients from systemic corticosteroid therapy.

Long-acting $beta_2$-adrenergic agonists may increase the risk of asthma-related death (see **WARNINGS**). Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on other asthma-controller medications (e.g., low-to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies. SYMBICORT is not indicated for patients whose asthma can be successfully managed by inhaled corticosteroids or other controller medications along with occasional use of inhaled short-acting $beta_2$-agonists.

SYMBICORT is available in 2 strengths, SYMBICORT 80/4.5 and SYMBICORT 160/4.5, containing 80 and 160 mcg of budesonide, respectively, and 4.5 mcg of formoterol fumarate dihydrate per inhalation. Each dose is administered as 2 inhalations twice daily (in the morning and the evening) by the orally inhaled route only. Rinsing the mouth after every dose is advised.

For patients who are currently receiving medium to high doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 160/4.5, 2 inhalations twice daily.

For patients who are currently receiving low to medium doses of inhaled corticosteroid therapy, and whose disease severity clearly warrants treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 80/4.5, 2 inhalations twice daily.

For patients who are not currently receiving inhaled corticosteroid therapy, but whose disease severity clearly warrants initiation of treatment with two maintenance therapies, the recommended starting dose is SYMBICORT 80/4.5 or 160/4.5, 2 inhalations twice daily depending upon asthma severity.

If a previously effective dosage regimen of SYMBICORT fails to provide adequate control of asthma, the therapeutic regimen should be reevaluated and additional therapeutic options, e.g., replacing the current strength of SYMBICORT with a higher strength, adding additional inhaled corticosteroid, or initiating oral corticosteroids, should be considered.

The maximum daily recommended dose is 640/18 mcg budesonide/formoterol (given as two inhalations of SYMBICORT 160/4.5 twice daily) for patients 12 years of age and older. Do not use more than twice daily or use a higher number of inhalations (more than 2 inhalations twice daily) of the prescribed strength of SYMBICORT as this will result in a daily dose of formoterol in excess of the dose determined to be safe. For all patients, consideration should be given to titrating to the lowest effective strength after adequate asthma stability has been achieved.

SYMBICORT is not approved for the treatment or prevention of exercise-induced bronchospasm. Patients who are receiving SYMBICORT twice daily should not use formoterol or other long-acting $beta_2$-agonists for prevention of exercise-induced bronchospasm, or for any

other reason. If symptoms arise in the period between doses, an inhaled, short-acting $beta_2$-agonist should be taken for immediate relief.

In clinical studies, significant improvement in FEV_1 occurred within 15 minutes of beginning treatment with SYMBICORT in most patients and improvement in asthma control (asthma symptoms, albuterol rescue use, PEF) occurred within one day. The maximum benefit may not be achieved for 2 weeks or longer after beginning treatment. Individual patients may experience a variable time to onset and degree of symptom relief.

For patients who do not respond adequately to the starting dose after 1-2 weeks of therapy with SYMBICORT 80/4.5, replacing the strength with SYMBICORT 160/4.5 may provide additional asthma control.

SYMBICORT should be primed before using for the first time by releasing 2 test sprays into the air away from the face, shaking well for 5 seconds before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well before each spray and releasing 2 test sprays into the air away from the face.

Geriatric Use

In studies where geriatric patients (65 years of age or older, see **PRECAUTIONS, Geriatric Use**) have been treated with SYMBICORT, efficacy and safety did not differ from that in younger patients. Based on available data for SYMBICORT and its active components, no dosage adjustment is recommended.

HOW SUPPLIED

SYMBICORT is available in two strengths:

SYMBICORT 80/4.5 (NDC 0186-0372-20) and **SYMBICORT 160/4.5 (NDC 0186-0370-20)**. Each strength is supplied as a pressurized aluminum canister with a shield component, with a red plastic actuator body with white mouthpiece and attached gray dust cap. Each canister contains 120 inhalations and has a net fill weight of 10.2 grams. Each canister is packaged in a foil overwrap pouch with desiccant sachet and placed into a carton. Each carton contains one canister and a Medication Guide.

The SYMBICORT canister should only be used with the SYMBICORT actuator and the SYMBICORT actuator should not be used with any other inhalation drug product.

The correct amount of medication in each inhalation cannot be ensured after the labeled number of inhalations from the canister have been used, even though the inhaler may not feel completely empty and may continue to operate. The inhaler should be discarded when the labeled number of inhalations have been used or within 3 months after removal from the foil pouch. Never immerse the canister into water to determine the amount remaining in the canister ("float test").

Store at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP]. Store the inhaler with the mouthpiece down.

For best results, the canister should be at room temperature before use. Shake well for 5 seconds before using.

Keep out of the reach of children. Avoid spraying in eyes. Contents under pressure. Do not puncture or incinerate. Do not store near heat or open flame. Exposure to temperatures over 120°F may cause bursting. Never throw container into fire or incinerator.

Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca Dunkerque Production, Dunkerque, France

Product of France
XXXXXX-00

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MEDICATION GUIDE

SYMBICORT 80/4.5

(budesonide 80 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

SYMBICORT 160/4.5

(budesonide 160 mcg and formoterol fumarate dihydrate 4.5 mcg) Inhalation Aerosol

Read the Medication Guide that comes with SYMBICORT before you start using it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about SYMBICORT?

- SYMBICORT contains 2 medicines:
  - Budesonide (the same medicine found in PULMICORT TURBUHALER®) an inhaled corticosteroid medicine. Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms.
  - Formoterol (the same medicine found in FORADIL® AEROLIZER®), a long-acting $beta_2$-agonist medicine or LABA. LABA medicines are used in patients with asthma. LABA medicines help the muscles around the airways in your lungs stay relaxed to prevent asthma symptoms, such as wheezing and shortness of breath. These symptoms can happen when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and may lead to death if not treated right away.

- **In patients with asthma, LABA medicines such as formoterol (one of the medicines in SYMBICORT) may increase the chance of death from asthma problems.** In a large asthma study, more patients who used another LABA medicine, died from asthma problems compared with patients who did not use that LABA medicine. Talk with your healthcare provider about this risk and the benefits of treating your asthma with SYMBICORT.

- **SYMBICORT does not relieve sudden symptoms. Always have an inhaled short-acting $beta_2$-agonist medicine with you to treat sudden symptoms. If you do not have this type of medicine, contact your healthcare provider to have one prescribed for you.**

- **Do not stop using SYMBICORT unless told to do so by your healthcare provider because your symptoms might get worse.**

- **SYMBICORT should be used only if your healthcare provider decides that another asthma-controller medicine alone does not control your asthma or that you need 2 asthma-controller medicines.**

- **Call your healthcare provider if breathing problems worsen over time while using SYMBICORT. You may need different treatment.**

- **Get emergency medical care if:**
  - **Breathing problems worsen quickly, and**
  - **You use your short-acting beta$_2$-agonist medicine, but it does not relieve your breathing problems.**

What is SYMBICORT?

SYMBICORT combines an inhaled corticosteroid medicine, budesonide (the same medicine found in PULMICORT TURBUHALER), and a long-acting beta$_2$-agonist medicine (LABA), formoterol (the same medicine found in FORADIL AEROLIZER).

SYMBICORT is used long-term, twice a day, everyday to control symptoms of asthma, and prevent symptoms such as wheezing in patients 12 years of age and older.

SYMBICORT contains formoterol (the same medicine found in FORADIL AEROLIZER). Because LABA medicines such as formoterol may increase the chance of death from asthma problems, SYMBICORT is not for patients with asthma who:

- are well controlled with another asthma-controller medicine such as a low to medium dose of an inhaled corticosteroid medicine
- only need short-acting beta$_2$-agonist medicines once in awhile

What should I tell my healthcare provider before using SYMBICORT?

Tell your healthcare provider about all of your health conditions, including if you:

- **have heart problems**
- **have high blood pressure**
- **have seizures**
- **have thyroid problems**
- **have diabetes**
- **have liver problems**
- **have osteoporosis**
- **have an immune system problem**
- **are pregnant or planning to become pregnant.** It is not known if SYMBICORT may harm your unborn baby.
- **are breastfeeding.** It is not known if SYMBICORT passes into your milk and if it can harm your baby.
- **are allergic to SYMBICORT or any other medicines**
- **are exposed to chickenpox or measles**

Tell your healthcare provider about all the medicines you take including prescription and non-prescription medicines, vitamins, and herbal supplements. SYMBICORT and certain other medicines may interact with each other. This may cause serious side effects.

Know all the medicines you take. Keep a list and show it to your healthcare provider and pharmacist each time you get a new medicine.

How do I use SYMBICORT?

See the step-by-step instructions for using SYMBICORT at the end of this Medication Guide. Do not use SYMBICORT unless your healthcare provider has taught you and you understand everything. Ask your healthcare provider or pharmacist if you have any questions.

- Use SYMBICORT exactly as prescribed. **Do not use SYMBICORT more often than prescribed.** SYMBICORT comes in 2 strengths. Your healthcare provider has prescribed the strength that is best for you.

- SYMBICORT should be taken as 2 puffs in the morning and 2 puffs in the evening every day. If you miss a dose of SYMBICORT, you should take your next dose at the same time you normally do. Do not take SYMBICORT more often or use more puffs than you have been prescribed.

- Rinse your mouth with water after each dose (2 puffs) of SYMBICORT.

- **While you are using SYMBICORT twice a day, do not use other medicines that contain a long-acting beta$_2$-agonist (LABA) for any reason, such as SEREVENT DISKUS (salmeterol xinafoate inhalation powder), ADVAIR DISKUS or ADVAIR HFA (fluticasone propionate and salmeterol), or FORADIL AEROLIZER (formoterol fumarate inhalation powder).**

- Do not change or stop any of your medicines used to control or treat your breathing problems. Your healthcare provider will adjust your medicines as needed.

- Make sure you always have a short-acting beta$_2$-agonist medicine with you. Use your short-acting beta$_2$-agonist medicine if you have breathing problems between doses of SYMBICORT.

- **Call your healthcare provider or get medical care right away if:**
  - your breathing problems worsen with SYMBICORT
  - you need to use your short-acting beta$_2$-agonist medicine more often than usual
  - your short-acting beta$_2$-agonist medicine does not work as well for you at relieving symptoms
  - you need to use 4 or more inhalations of your short-acting beta$_2$-agonist medicine for 2 or more days in a row
  - you use 1 whole canister of your short-acting beta$_2$-agonist medicine in 8 weeks' time
  - your peak flow meter results decrease. Your healthcare provider will tell you the numbers that are right for you.
  - your asthma symptoms do not improve after using SYMBICORT regularly for 1 week.

What are the possible side effects with SYMBICORT?

SYMBICORT contains formoterol. In patients with asthma, LABA medicines such as formoterol may increase the chance of death from asthma problems. See "What is the most important information I should know about SYMBICORT?"

Other possible side effects with SYMBICORT include:

- **serious allergic reactions including rash, hives, swelling of the face, mouth, and tongue, and breathing problems.** Call your healthcare provider or get emergency medical care if you get any symptoms of a serious allergic reaction.
- **chest pain**
- **increased blood pressure**
- **a fast and irregular heartbeat**
- **headache**
- **tremor**
- **nervousness**
- **immune system effects and a higher chance for infections**
- **eye problems including glaucoma and cataracts.** Regular eye exams should be considered while using SYMBICORT.
- **lower bone mineral density.** This may be a problem for people who already have a higher chance for low bone mineral density (osteoporosis).
- **slowed growth in children.** A child's growth should be checked often.
- **throat irritation.**

Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the side effects with SYMBICORT. Ask your healthcare provider or pharmacist for more information.

How do I store SYMBICORT?

- Store SYMBICORT at room temperature 68°F to 77°F (20°C to 25°C). Store with the mouthpiece down.

- The contents of your SYMBICORT canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120°F may cause the canister to burst.

- **Keep SYMBICORT and all medicines out of the reach of children.**

General Information about SYMBICORT

Medicines are sometimes prescribed for purposes not mentioned in a Medication Guide. Do not use SYMBICORT for a condition for which it was not prescribed. Do not give your SYMBICORT to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about SYMBICORT. If you would like more information, talk with your healthcare provider or pharmacist. You can ask your healthcare provider or pharmacist for information about SYMBICORT that was written for healthcare professionals. You can also contact the company that makes SYMBICORT (toll free) at 1-800-236-9933 or visit our website at www.symbicort-us.com.

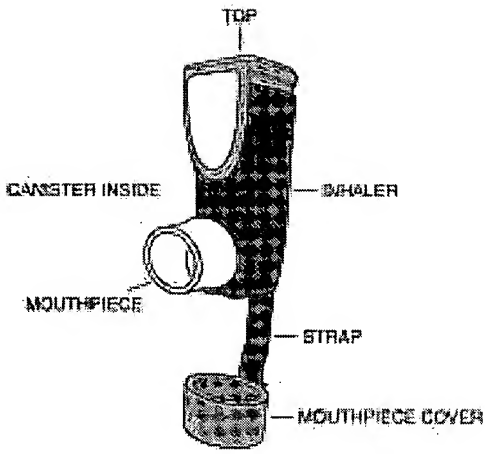

Figure 1

HOW TO USE SYMBICORT

Follow the instructions below for using SYMBICORT. You will breathe-in (inhale) the medicine. If you have any questions, ask your doctor or pharmacist.

PREPARING YOUR INHALER FOR USE

1. Take your SYMBICORT inhaler out of the moisture-protective foil pouch before you use it for the first time and throw the foil away. Write the date that you open the foil pouch on the dose tracker card that comes with your inhaler. You should discard the inhaler when the labeled number of inhalations have been used or within 3 months of opening the foil pouch.

2. Use the SYMBICORT canister only with the red SYMBICORT inhaler supplied with the product. Parts of the SYMBICORT inhaler should not be used with parts from any other inhalation drug product.

3. SHAKE THE INHALER WELL for 5 seconds right before each use. Remove the mouthpiece cover. Check the mouthpiece for foreign objects prior to use.

4. SYMBICORT should be primed before using it for the first time and also when the inhaler has not been used for more than 7 days. Prime the inhaler by shaking the inhaler well for 5 seconds and then releasing a test spray. Then shake the inhaler again and release a second test spray. Your inhaler is now primed and ready for use.

Do not spray the medicine in your eyes during priming or use.

WAYS TO HOLD THE INHALER FOR USE

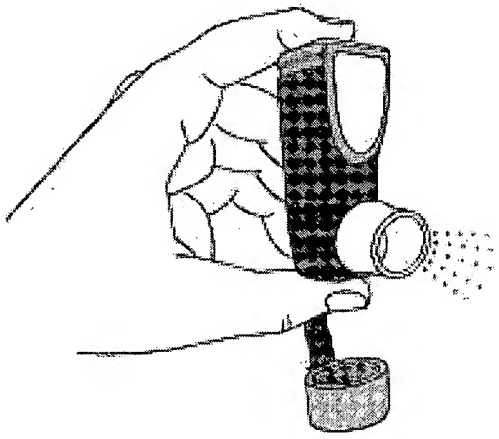

Figure 2

OR

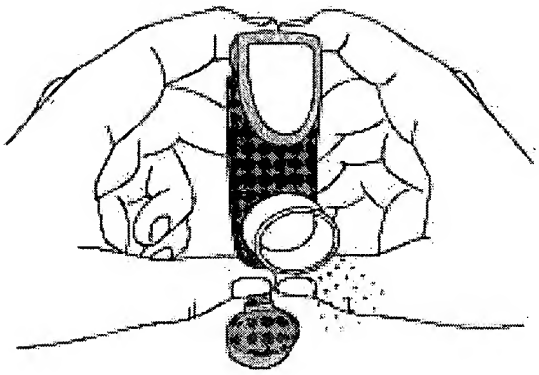

Figure 3

USING YOUR SYMBICORT INHALER

5. SHAKE THE INHALER WELL for 5 seconds. Remove the mouthpiece cover. Check the mouthpiece for foreign objects.

6. Breathe out fully (exhale). Raise the inhaler up to your mouth. Place the white mouthpiece fully into your mouth and close your lips around it. Make sure that the inhaler is upright and that the opening of the mouthpiece is pointing towards the back of your throat (see Figure 4).

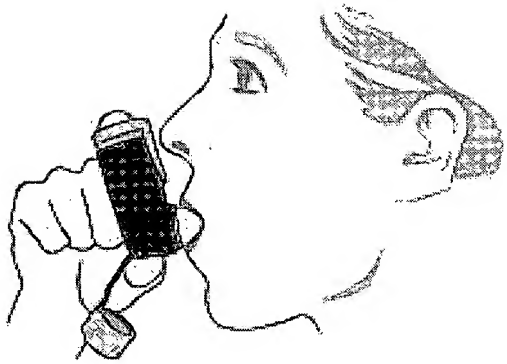

Figure 4

7. While breathing in deeply and slowly through your mouth, press down firmly and fully on the grey top of the inhaler to release the medicine (see Figures 2 and 3).

8. Continue to breathe in and hold your breath for about 10 seconds, or for as long as is comfortable. Before breathing out, release your finger from the grey top and remove the inhaler from your mouth while keeping the inhaler upright.

9. Shake the inhaler again for 5 seconds and repeat steps 6 through 8.

AFTER USING YOUR SYMBICORT INHALER

10. Replace the mouthpiece cover after use.

11. After you finish taking this medicine (2 puffs), rinse your mouth with water. Spit out the water. Do not swallow it.

12. Use the enclosed dose tracker card to track the number of puffs you have taken by marking off or punching through each of your morning and evening doses.

OTHER IMPORTANT INFORMATION ABOUT YOUR SYMBICORT INHALER

It is very important that you keep track of the number of inhalations (puffs) you have taken from your SYMBICORT inhaler. Discard SYMBICORT after you have used the number of inhalations on the product label and box. Your inhaler may not feel empty, but you will not get the right amount of medicine if you keep using it.

SYMBICORT should also be discarded within 3 months after it is taken out of its foil pouch.

- For best results, use and store at room temperature. Avoid exposing product to extreme heat and cold. Store with the mouthpiece down.

HOW TO CLEAN YOUR SYMBICORT INHALER

Clean the white mouthpiece of the inhaler every 7 days. To clean the mouthpiece:

- Remove the grey mouthpiece cover
- Wipe the inside and outside of the white mouthpiece opening with a clean, dry cloth
- Replace the mouthpiece cover
- **Do not put the inhaler into water**
- Do not try to take the inhaler apart

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Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Dunkerque, France

Product of France

XXXXXX-00
Rev 07/20/06

This Medication Guide has been approved by the U.S. Food and Drug Administration.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-929

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Mark DeSiato
Director, Regulatory Affairs

Dear Mr. DeSiato:

Please refer to your new drug application (NDA) dated September 23, 2005, received September 23, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol.

We acknowledge receipt of your submissions dated October 21, November 2, 8, and 29, and December 8, 15 (2), 19, and 27, 2005, and January 19, and 30, March 16 (2) and 17 (2), April 11, 13, 19, 26, and 27, May 9, 10, 15 (2), and 31, June 1, 14, 16, and 27, and July 11, 12, 17, 19, and 20, 2006.

This new drug application provides for the use of SYMBICORT® for the long term maintenance treatment of asthma in patients 12 years of age and older.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert [copy enclosed] and Medication Guide[copy enclosed] submitted July 20, 2006, the immediate container label submitted July 11, 2006, and the foil, shield, and carton label submitted July 20, 2006). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-929.**" Approval of this submission by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies in patients 6 to less than 12 years of age until December

31, 2007. We are waiving the pediatric study requirement for pediatric patients ages zero to less than 6 years of age.

We remind you of your post-approval Chemistry, Manufacturing, and Controls agreements as listed in your amendment dated July 12, 2006.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Colette Jackson, Regulatory Project Manager, at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Director
Division of Pulmonary and Allergy Products
Office of Drug Evaluation II
Center For Drug Evaluation and Research

Enclosure: Package Insert and Medication Guide.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Badrul Chowdhury
7/21/2006 04:36:00 PM

AstraZeneca

19 September 2006

The Synergistic Effect of SYMBICORT®

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1. INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by episodes of reversible airflow obstruction leading to wheezing, breathlessness, chest tightness, and cough. Budesonide, an inhaled corticosteroid (ICS) with anti-inflammatory properties, and formoterol, a long-acting β_2-agonist (LABA) bronchodilator, are two important and pharmacologically distinct medications for asthma.

The preclinical and clinical data summarized herewith demonstrate the synergistic interaction between budesonide and formoterol and the clinical benefit of this relationship when budesonide and formoterol are administered in combination in patients with asthma.

2. EVIDENCE OF SYNERGY FROM PRECLINICAL STUDIES

Studies using cell cultures as well as animal models demonstrate that administration of budesonide and formoterol together can lead to a complementary effect such that the resultant pharmacologic effects are greater than the sum of their parts.

Information from cell culture models

- **Airway smooth muscle cells** – In asthma, because of altered cellular signaling, airway smooth muscle cells proliferate and change to a synthetic phenotype. This causes thickening of the airway wall and leads to airway obstruction. Therefore, there is a large benefit for therapy to address smooth muscle proliferation. Roth et al (2002) demonstrated that budesonide and formoterol are each active against smooth muscle proliferation, but the combination delivers a 100-fold synergy.

- **Fibroblasts** – Fibroblasts create extracellular matrix and scar tissue. They are activated in asthma and contribute to the development of airway obstruction. The combination of budesonide and formoterol inhibits the activation of fibroblasts and resultant secretion of extracellular matrix proteoglycans more effectively than either component alone (Todorova et al 2006).

- **Inflammatory cells (eosinophils, monocytes)** – Inflammatory cells infiltrate lung tissues and underly exacerbations and remodeling by the secretion of toxic substances and immunological mediators. There are many examples of synergy demonstrated by the effect of the combination on these cell types, including eosinophils, which are regarded as critical to pathogenesis. For instance, the combination of budesonide and formoterol exhibits synergy with respect to suppression of eosinophil oxidative burst (an example of toxic substance release in inflammation) (Miller-Larsson et al 2001, Persdotter et al 2005). In monocytes, formoterol promotes steroid receptor translocation to the cell nucleus, a process that can increase the sensitivity of the cells to the anti-inflammatory effects of steroids (Yanagawa et al 2001).

Information from animal models

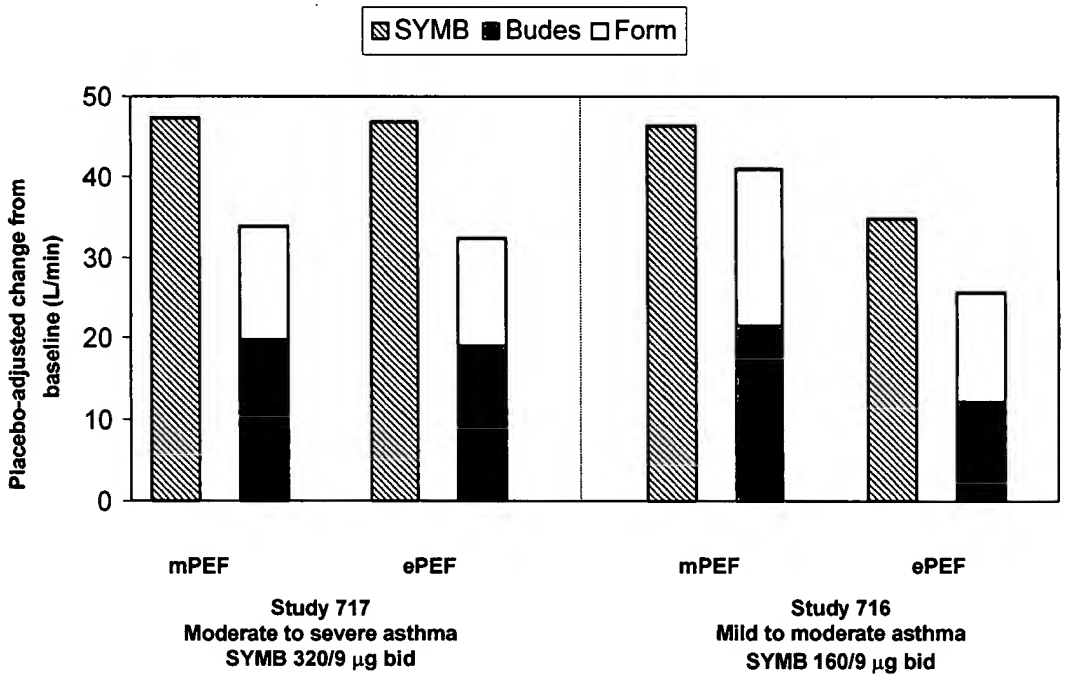
In a rat model, low-dose budesonide (10 nmol/kg) in combination with low-dose formoterol (0.3 nmol/kg) synergistically reduced lung edema by 47%, which is more than twice the sum of the non-significant reductions seen with budesonide (6%) and formoterol (13%) alone, and equal to the effects produced by much higher doses of either drug alone (300 nmol/kg budesonide or 2.0 nmol/kg formoterol) (Lindahl et al 2002, Miller-Larsson and Brattsand 2004). The combination of budesonide and formoterol also synergistically decreased the proinflammatory cytokine IL-1β concentration in the tissue by 42%, while neither budesonide (10 nmol/kg) nor formoterol (0.3 nmol/kg) had any effect at all (Miller-Larsson and Brattsand 2004). It is also known that cytokine stimulation can depress the effect of β_2-adrenergic receptor signaling; however, in IL-1β and TNFα-stimulated mouse trachea, budesonide restores the relaxant effect of formoterol (Adner et al 2006).

Similar data showing synergistic reduction of lung inflammation in rats appears in the declarations of inventor Jan William Trofast, submitted during prosecution of the '860 patent for which term extension is sought. These declarations, submitted under 37 C.F.R. §1.132, are attached.

3. CLINICAL EVIDENCE OF SYNERGY: BENEFITS OF SYMBICORT VERSUS ITS MONOCOMPONENTS

Clinical evidence of the synergy seen with budesonide and formoterol administered as SYMBICORT is best illustrated by results of two pivotal US studies that form the basis of the US NDA submitted September 2005 (Figure 1) and which are discussed in further detail in this section.

Figure 1 **Morning and evening PEF: placebo-adjusted change from baseline to the average during double-blind treatment (Studies 717 and 716)**



SYMB -SYMBICORT pMDI; Budes - budesonide pMDI (320 µg bid Study 717, 160 µg bid Study 716); Form - formoterol TBH (9 µg bid)
mPEF - Morning peak expiratory flow; ePEF - Evening peak expiratory flow; bid - Twice daily.

The first demonstration of the clinical benefits of combination therapy with budesonide and formoterol was shown in two landmark clinical studies, FACET and OPTIMA.

As initially shown in the FACET study (Pauwels et al 1997), the combination of formoterol and budesonide provides better control of symptoms and further improvement in lung function compared to budesonide alone in patients with moderate to severe asthma, thus allowing equivalent or better asthma control at lower doses of inhaled corticosteroids (ICS).

The OPTIMA study (O'Byrne et al 2001) extended the findings of the FACET study and showed that severe asthma exacerbations were more effectively reduced with budesonide and formoterol treatment than with a higher dose of budesonide alone in patients with mild to

moderate asthma. The study evaluated treatment with budesonide 100 or 200 μg twice daily (bid) either alone or with formoterol 4.5 μg bid for twelve months. Addition of formoterol to a low dose of budesonide was more effective than a two-fold higher dose of budesonide at reducing the rate of severe exacerbations in these patients. Adding formoterol to either a low or high dose of budesonide reduced the rate of severe exacerbations by an average of 51%. Moreover, the addition of budesonide to formoterol during an acute episode of bronchoconstriction has been found to reverse tolerance to chronic LABA monotherapy (Aziz and Lipworth 1999).

While the FACET and OPTIMA studies examined the effects of adding formoterol to budesonide therapy (*i.e.*, by comparing budesonide/formoterol to budesonide alone), Studies 716 and 717 are the first to demonstrate the effects of each separate monoproduct in comparison to the combination product. These two pivotal randomized, double-blind, placebo-controlled studies formed the basis of the recent approval of SYMBICORT in the U.S. Each study evaluated twice-daily doses of SYMBICORT in comparison with the comparable dose of each monoproduct and placebo over a twelve-week treatment period. Study 716 was conducted in mild to moderate persistent asthmatics and evaluated a SYMBICORT dose (budesonide/formoterol) of 160/9 μg bid; Study 717 was conducted in moderate to severe persistent asthmatics and evaluated a SYMBICORT dose of 320/9 μg bid. The inclusion of the two monocomponent arms facilitates the demonstration of synergy between budesonide and formoterol.

In Studies 716 and 717, a co-primary endpoint was pre-dose FEV_1*, recorded at each of three clinic visits during the twelve-week treatment period in each study. In both studies, for the measure of improvement in pre-dose FEV_1, there were numeric differences in favor of SYMBICORT compared to the effect of each monoproduct added together for patients receiving twelve weeks of treatment (Table 1 and Table 2). Similar findings were observed in Study 717 (conducted in moderate to severe persistent asthmatics) for all patients at end of treatment, regardless of the time of study withdrawal (Table 1).

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* FEV_1 is the forced expiratory volume in the first second, a measure of lung function recorded via spirometry at the clinic prior to administration of SYMBICORT.

Table 1 **Pre-dose FEV_1: placebo-adjusted change from baseline at end of treatment and at Week 12 (Study 717)**

	Placebo-adjusted change from baseline (L) [a]	
	LS mean (SEM)	**95% CI**
End of treatment [b]		
SYMBICORT	0.37 (0.05)	(0.27, 0.47)
Budesonide	0.27 (0.05)	(0.16, 0.37)
Formoterol	0.06 (0.05)	(-0.04, 0.17)
Week 12		
SYMBICORT	0.23 (0.06)	(0.11, 0.34)
Budesonide	0.16 (0.06)	(0.04, 0.28)
Formoterol	0.05 (0.06)	(-0.08, 0.17)

[a] Change from baseline for each treatment versus placebo.
[b] End of treatment refers to the last available visit (*i.e.*, may be earlier than Week 12 for patients who discontinued the study prematurely).
Doses administered: SYMBICORT pMDI 320/9 µg bid; budesonide pMDI 320 µg bid; formoterol TBH 9 µg bid.
From Tables 35 and 37 of the Clinical Study Report (CSR) for Study 717.

Table 2 **Pre-dose FEV_1: placebo-adjusted change from baseline at end of treatment and at Week 12 (Study 716)**

	Placebo-adjusted change from baseline (L) [a]	
	LS mean (SEM)	**95% CI**
End of treatment [b]		
SYMBICORT	0.34 (0.05)	(0.23, 0.45)
Budesonide	0.19 (0.06)	(0.08, 0.29)
Formoterol	0.14 (0.06)	(0.03, 0.25)
Week 12		
SYMBICORT	0.23 (0.06)	(0.11, 0.35)
Budesonide	0.08 (0.06)	(-0.04, 0.21)
Formoterol	0.10 (0.07)	(-0.03, 0.23)

[a] Change from baseline for each treatment versus placebo.
[b] End of treatment refers to the last available visit (*i.e.*, may be earlier than Week 12 for patients who discontinued the study prematurely).
Doses administered: SYMBICORT pMDI 160/9 µg bid; budesonide pMDI 160 µg bid; formoterol TBH 9 µg bid.
From Tables 36 and 38 of the CSR for Study 716.

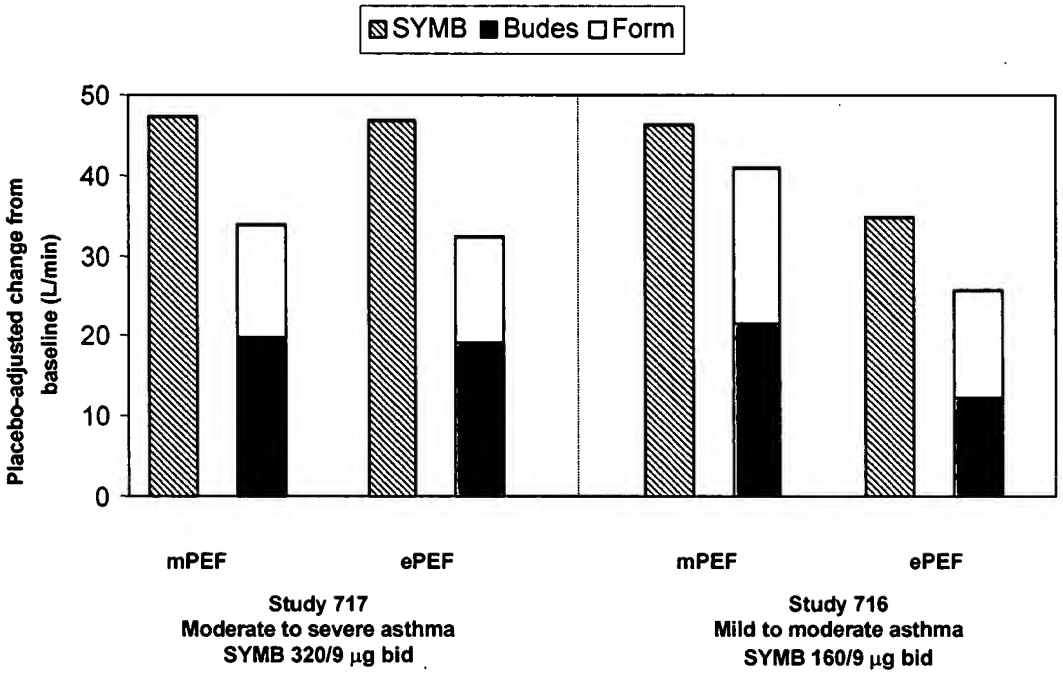
In Studies 717 and 716, an additional lung function measure, peak expiratory flow (PEF), was collected by the patient at home before taking study drug. As morning and evening PEF yielded more data available for analysis, it was felt that these data may represent a potentially

more sensitive lung function measure with which to evaluate trends observed for pre-dose FEV_1. This is particularly important as both studies utilized sensitive asthma worsening criteria designed to quickly withdraw patients with worsening asthma (predominantly anticipated in the formoterol and placebo arms). As a result, patients who withdrew before completing the twelve-week treatment period were likely to have fewer than the three scheduled on-treatment FEV_1 assessments, thus limiting the available data for this variable.

In Study 717, a more-than-additive benefit of SYMBICORT in comparison with the sum of treatment with the monoproducts was clearly demonstrated for morning and evening PEF – *i.e.*, the effect with each monoproduct (as compared to placebo) was less than half that seen with SYMBICORT. Similar results were seen in Study 716, where the effect on morning and evening PEF was more pronounced with SYMBICORT compared to the combined effects of the two monoproducts.

These results show the synergistic effects of SYMBICORT on PEF and are graphically depicted in Figure 1 (repeated below) and summarized in Table 3 (Study 717) and Table 4 (Study 716).

Fig. 1 (repeated) Morning and evening PEF: placebo-adjusted change from baseline to the average during double-blind treatment (Studies 717 and 716)



SYMB -SYMBICORT pMDI; Budes - budesonide pMDI (320 µg bid Study 717, 160 µg bid Study 716); Form - formoterol TBH (9 µg bid)
mPEF - Morning peak expiratory flow; ePEF - Evening peak expiratory flow; bid - Twice daily.

Table 3 **Morning and evening PEF: placebo-adjusted change from baseline to the average during double-blind treatment (Study 717)**

	Placebo-adjusted change from baseline (L/min) [a]	
	LS mean (SEM)	**95% CI**
Morning PEF		
SYMBICORT	47.42 (4.16)	(39.24, 55.60)
Budesonide	19.95 (4.26)	(11.57, 28.33)
Formoterol	13.85 (4.19)	(5.62, 22.08)
Evening PEF		
SYMBICORT	46.84 (4.29)	(38.41, 55.27)
Budesonide	19.02 (4.40)	(10.38, 27.66)
Formoterol	13.37 (4.31)	(4.91, 21.83)

[a] Change from baseline to the average during double-blind treatment for each treatment versus placebo.
Doses administered: SYMBICORT pMDI 320/9 µg bid; budesonide pMDI 320 µg bid; formoterol TBH 9 µg bid.
From Table 54 of the CSR for Study 717.

Table 4 **Morning and evening PEF: placebo-adjusted change from baseline to the average during double-blind treatment (Study 716)**

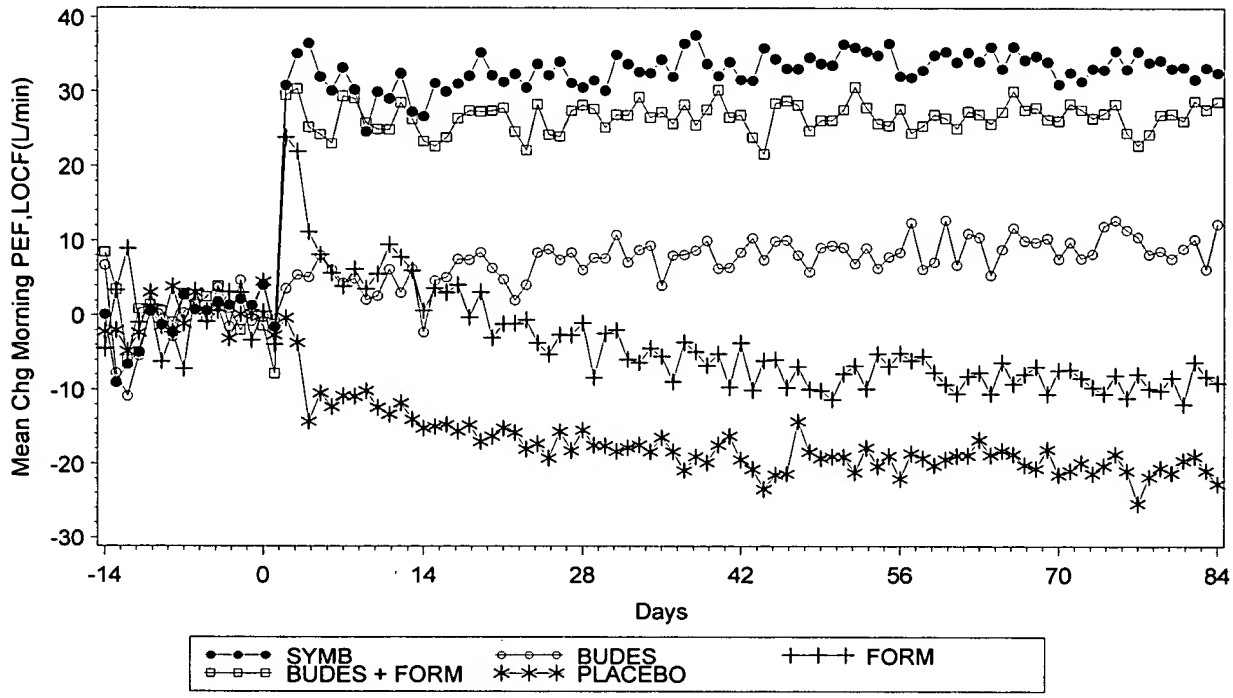
	Placebo-adjusted change from baseline (L/min) [a]	
	LS mean (SEM)	**95% CI**
Morning PEF		
SYMBICORT	46.42 (4.83)	(36.93, 55.91)
Budesonide	21.47 (4.86)	(11.90, 31.03)
Formoterol	19.42 (4.99)	(9.62, 29.23)
Evening PEF		
SYMBICORT	34.84 (4.45)	(26.09, 43.58)
Budesonide	12.36 (4.48)	(3.55, 21.17)
Formoterol	13.49 (4.60)	(4.45, 22.52)

[a] Change from baseline to the average during double-blind treatment for each treatment (SYMBICORT, budesonide, and formoterol) versus placebo.
Doses administered: SYMBICORT pMDI 160/9 µg bid; budesonide pMDI 160 µg bid; and formoterol TBH 9 µg bid.
From Table 57 of the CSR for Study 716.

As shown in Figure 2, the effect on morning PEF seen with SYMBICORT and with the sequential administration of budesonide and formoterol in Study 717 was evident within 1 day of the first dose and persisted throughout the twelve weeks of study treatment. In contrast, an

anticipated decrease in the initial benefit (*i.e.*, tolerance) was observed soon after initiation of treatment with formoterol alone. This prevention of tolerance to the effect of formoterol monotherapy, particularly in moderate to severe asthmatics, is a critically important aspect of the synergistic effect of the combination of budesonide and formoterol. Similar findings were observed for evening PEF in Study 717 and for both morning and evening PEF in Study 716.

Figure 2 Mean change from baseline in morning PEF by study day (Study 717)



SYMB- SYMBICORT pMDI 320/9 µg bid; Budes- budesonide pMDI 320 µg bid; Form- formoterol TBH 9 µg bid; Budes+Form budesonide pMDI 320 µg bid plus formoterol TBH 9 µg bid; Placebo bid.
LOCF Last observation carried forward; PEF Peak expiratory flow.
From Figure 14 of the CSR for Study 717.

A critical objective of the NDA registration program was to demonstrate that the clinical benefits of SYMBICORT compared to formoterol and budesonide were not due to differences in the devices used. This was important as SYMBICORT and budesonide were administered via a pressurized meter dose inhaler (pMDI) and formoterol was administered via a dry powder inhaler (TBH). This was successfully accomplished in a study specifically designed to demonstrate the pharmacodynamic equivalence of formoterol administered via the two devices (Study 729) and by the comparable results of the SYMBICORT and budesonide+formoterol arms in Study 717 (Figure 2).

Evidence indicating that pharmacokinetic (PK*) effects are not responsible for the clinical synergistic effects seen with SYMBICORT comes from two PK studies (Studies 721 and 722). These studies indicate that there is no PK interaction between budesonide and formoterol and that the clinical benefits of SYMBICORT are not due to increased exposure to budesonide and formoterol compared to the monocomponents.

In conclusion, these data demonstrate a synergistic effect following administration of the budesonide and formoterol monocomponents together as SYMBICORT relative to administration of each individual monocomponent administered alone.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : C. Carling, et al.

Serial No. : 08/317,407

Filed : October 3, 1994

For : COMBINATION OF A BRONCHODILATOR AND STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS, AS WELL AS ITS USE AND THE PREPARATION THEREOF

DECLARATION UNDER 37 C.F.R. § 1.132

I, Jan William Trofast, Ph.D., declare as follows:

I am Principal Research Scientist in Pharmaceutical and Analytical Research and Development at Astra Draco AB in Lund, Sweden, a subsidiary of Astra AB, the assignee of the above-identified application. My curriculum vitae is attached as Exhibit A.

I am a coinventor of the subject matter of the above-identified patent application, and I participated in the August 17, 1994 Examiner interview. I am familiar with the office actions issued during the course of prosecution of this application and its parent, as well as the prior art patents of Brattsand, et al. and Murakami, et al. cited against the pending claims.

A Declaration under 37 C.F.R. § 1.132, signed by me on May 24, 1995, was submitted on June 9, 1995 as a follow-up to Applicants' May 23, 1995 Amendment and Response. In the subsequent office action of August 30, 1995, the Examiner asserted that the data set forth in the Declaration are not sufficient to demonstrate nonobviousness over the cited prior art because they are not commensurate in scope with the invention as claimed. In response to the Examiner's assertion, the pharmacological *in vivo* studies set forth below were performed; they were carried out at my behest by pharmacologists at Astra Draco AB.

The data set forth in the previous Declaration demonstrated the synergistic potency of combinations of formoterol and budesonide in molar ratios ranging from 1:1 to 1:20 in reducing lung inflammation. The new data presented herein were obtained from tests in which a formoterol-budesonide combination in a 1:60 molar ratio of the two active ingredients was administered. The new tests were performed using the same Sephadex-induced edema model in rats according to the protocols set forth in the May 24, 1995 Declaration. The new results are presented in Table I below:

TABLE I

Inhibition of Sephadex-Induced Lung Inflammation in Rats

Compound	Amount Administered (nmol/kg)	n†	% inhibition
1. Budesonide	120	6	21
2. Formoterol + Budesonide (1:60)	2 + 120	6	69* (p=0.0104)

† number of animals subjected to regimen

Statistical parameters: * $p<0.05$; ** $p<0.01$

The inhibition of inflammation by formoterol administered alone at 2 nmol/kg was taken to be 13%, the value previously determined in tests of 12 animals and set forth in the May 24, 1995 Declaration.

As in the previously performed tests with formoterol-budesonide combinations, the statistical analysis was obtained by comparing the effect of the given combination with the effect of the corresponding amount of budesonide administered without formoterol. This type of analysis was designed to particularly point up enhanced anti-inflammatory effects of the combination in comparison to the effects expected (and observed) for the anti-inflammatory steroid (budesonide) component alone.

In the previously performed tests, it was observed that budesonide by itself in a concentration range from 5 nmol/kg to 40 nmol/kg produced no significant inhibition of Sephadex-induced edema in the rat. From Table I above it can be seen that even a dosage of 120 nmol/kg of budesonide alone gave only 21% inhibition of inflammation; this is insignificant compared to that observed with administration of a placebo. As before, however, the effect of formoterol and budesonide in combination (69% inhibition) was seen unquestionably to be significant ($p=0.0104$), based on the criterion of the Wilcoxon rank sum test, and far greater than the sum of the individual effects of each of the components.

It is known in the pharmacology art that rat cells exhibit 3-10 times greater sensitivity to glucocorticosteroids than does man, although this could differ to some extent in *in vivo* test models. The work of Claman, New England J. Med. 287, 388-397 (1972), copy attached as Exhibit B, is representative of the knowledge in the field. Particular attention is called to Table 2 of Claman and the text under "SPECIES DIFFERENCES" on pages 388-389.

The effect of administration of a 1:60 molar ratio of formoterol to budesonide in the instant rat test regimen, then, can be taken to be reflective of the effect

of a 1:200 or lower molar ratio of the two active ingredients administered to a human subject.

It should be emphasized that it would be difficult to demonstrate a statistically significant synergistic effect of, for example, an actual 1:200 ratio of formoterol to budesonide in the rat (as opposed to the 1:60 ratio in the rat which is reflective of a 1:200 ratio in a human); because of the heightened sensitivity of the rat, budesonide at such a high dosage would have a significant effect by itself. Conversely, if one were to take into account the heightened sensitivity of the rat by decreasing the dosage of formoterol in order to achieve the lower formoterol-to-budesonide ratio, the resultant formoterol dosage would be too low to have an effect, not just alone but even in combination with budesonide; the lower limit of activity must always be considered in administration of a therapeutic agent.

The data herein provide further demonstration that budesonide-formoterol combinations over a wide range of molar ratios provide an enhancement of anti-inflammatory effect which, unexpectedly, is significantly greater than the sum of the individual anti-inflammatory effects of the two active agents. More precisely, the data herein, as well as those set forth in the previous Declaration,

demonstrate that neither budesonide without formoterol nor formoterol without budesonide provide significant reduction of Sephadex-induced inflammation at the administered concentrations. On the other hand, treatment of animals with the combined agents in the same concentrations administered individually resulted in unquestionable, significant reduction of inflammation.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: June 19 Dec. 1995

Jan W. Trofast
JAN W. TROFAST, Ph.D.

EXHIBIT A

ASTRA
ASTRA DRACO

CURRICULUM VITAE

NAME:	Trofast Jan William
DATE OF BIRTH:	13 September 1946
NATIONALITY:	Swedish
EDUCATION AND/OR ACADEMIC DEGREE:	Master of Science (Chemical Engineering), 1969 Lund Institute of Technology Master of Art (Chemistry), Univ. of California 1971 Doctor of Philosophy (Organic Chemistry), 1978 Lund Institute of Technology Course in pharmacology for medical students, 1976 Univ. of Lund Course in fermentation, Univ of Lund 1977
PREVIOUS POSITIONS:	Ass. Director in Medicinal Chemistry 1979-91 Astra Draco Information Technology Astra Draco 1991-93 (Literature, patents)
PRESENT POSITION/ DEPARTMENT:	Principal Research Scientist at Pharmaceutical 1993- and Analytical R&D, Astra Draco
PUBLICATIONS:	See enclosure

DATE: 19 September 1994

Signature

Initials (JT)

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    4. Novel 16,17-acetalsubstituted pregnane 21-oic acid derivatives (priority date 851219)

5. New process (priority date 900926)
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Lund, September 19, 1994

Jan Trofast

EXHIBIT B

MEDICAL PROGRESS

CORTICOSTEROIDS AND LYMPHOID CELLS

HENRY N. CLAMAN, M.D.

GLUCOCORTICOSTEROID hormones of the adrenal cortex have striking pharmacologic effects on lymphoid tissues and cells. These effects form part of the basis for the widespread use of these hormones in the treatment of a variety of diseases involving immunologic, inflammatory or neoplastic processes. The subject is large and has been reviewed in the past,[1-7] but many questions remain to be answered.

The purpose of this article is to take a new look at the subject, concentrating on three aspects. The first is *species differences* in susceptibility to corticosteroids. (Although these differences have been noted before, they are often overlooked; they are of crucial importance in interpretation of data and, therefore, should be re-emphasized.) The second aspect consists in newer facts concerning the *heterogeneity of lymphoid cells* even within the same species. Such knowledge clarifies many of the contradictory statements about corticosteroids and lymphoid cells. Finally, attention is paid to recent advances in the study of the subcellular effects of corticosteroids on lymphoid cells, emphasizing *biochemical events* and *specific corticosteroid receptors*. Because of the enormous literature on the subject, this article is selective, not comprehensive.

CHEMICAL AND PHYSICAL CHARACTERISTICS OF GLUCOCORTICOSTEROIDS

Early studies were performed with crude adrenocortical extract, but recent work has used a wide variety of purified compounds. Dougherty et al.[3] have summarized the characteristics of glucocorticosteroids that are active on lymphoid tissues: an unsaturated A ring; a ketone at position 3; an O or OH at position 11; and a C=O, CH_2OH group at positions 20 and 21.

This family of glucocorticosteroids contains the hormones that are most potent in affecting the lymphoid tissues, and it is this group that is considered in this article. For convenience, the hormone family will here be termed merely "steroids." A number of natural and synthetic congeners exist.[8] With respect to the lymphoid system, these related compounds differ mainly in relative potency and do not show any fundamental differences in biologic effects.

Many of these steroids are available both in relatively water-soluble and in water-insoluble forms. Hydrocortisone (cortisol), for example, is often used in vivo as the acetate, which is rather insoluble, is slowly absorbed and therefore has a "depot effect." In vitro experiments, on the other hand, often use highly soluble salts, such as cortisol sodium succinate. If such soluble compounds are used in vivo, however, in dosages roughly equivalent to those of insoluble compounds, effects may be difficult to see[9,10] unless very large amounts[11] or repeated administration is used.[12]

For convenience, Table 1 compares molecular weights, molar concentrations and weight-volume characteristics of some steroids. Cortisol is the main adrenal glucocorticosteroid in man. The normal plasma cortisol level varies diurnally between about 0.04 and 0.2 μg per milliliter. An infusion of 40 mg of cortisol (equivalent to 10 mg of prednisone) will raise the plasma level to about 0.4 to 1.3 μg per milliliter.[13] This increase of six to 10 times is equivalent to a plasma cortisol concentration of about $1 - 4 \times 10^{-6}$M and exceeds the plasma binding capacity for cortisol. The biologic half-life for exogenous steroids is about 120 minutes. These facts are useful in analyzing in vitro data about the effects of steroids on lymphoid cells.

Table 1. Approximate Molecular Weights of Commonly Used Glucocorticosteroids and Selected Salts, and Comparison of Molar Concentrations and Weight/Volume Equivalents for Cortisol.

	Molecular Weight
a) Cortisone, hydrocortisone (cortisol), prednisone, prednisolone	358-362
b) Cortisone acetate, cortisol acetate	402-404
c) Cortisol succinate (Na), prednisolone phosphate (Na)	484

For cortisol (M W = 362)

Molar Concentration	Wt/Volume	
1	362.0 mg/ml	
10^{-1}	36.0	
10^{-2}	3.6	
10^{-3} (1mM)	362.0 μg/ml	
10^{-4}	36.0	
10^{-5}	3.6	pharmacologic plasma level
10^{-6} (1μM)	0.36	physiologic plasma level (4-16 μg/100 ml)
10^{-7}	0.036	

SPECIES DIFFERENCES

There are remarkable differences in susceptibility to glucocorticosteroids between various species.[14,15] The exact basis of these differences is not known, but animal species have been divided into steroid-sensitive and steroid-resistant groups (Table 2). The differentiation is usually based on the relative ease of producing lymphoid depletion after a given regimen of systemic glucocorticosteroids. The differentiation is of great importance. As it happens,

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Table 2. Glucocorticosteroid Sensitivities of Various Species.

Hamster Mouse Rat Rabbit	Sensitive	Ferret Monkey Guinea pig Man	Resistant

most of the information on the effects of steroids on lymphoid cells and immunologic processes has been gathered from experiments in steroid-sensitive species. Therefore, extrapolation of the results of these experiments to man (a steroid-resistant species) should be done with caution.

Corticosteroid-Sensitive Species

These species include the mouse, rat, hamster and rabbit. In these animals, the most dramatic result of the systemic administration of steroids is a rapid decrease in thymic weight.[14] This depletion is associated with intrathymic cell death as shown by vital staining[16] and electron microscopy.[12,17] Thymus cells from these species are also visibly damaged after in vitro culture with steroids for several hours at concentrations as low as 2.7×10^{-7}M.[18-20] Steroids also profoundly affect "peripheral lymphoid tissues." The animals exhibit lymphopenia[21,22] as well as shrinkage of the spleen and lymph nodes. In vitro studies also show that rat and rabbit peripheral blood lymphocytes and rat lymph-node cells are sensitive to steroids at concentrations of 2×10^{-7} to 2×10^{-3}M.[23-25]

Corticosteroid-Resistant Species

These include the guinea pig, monkeys and man. In guinea pigs, cortisone acetate given daily for seven days at a dose of 50 mg per kilogram per dose produced only a 37 per cent reduction in thymic weight.[18] By contrast, a single dose of this magnitude given to mice decreased the size of the thymus 90 per cent in one day.[27] Doses of corticosteroids in this range given singly[28] or repeatedly[29] produce little or no change in the peripheral lymphocyte count of guinea pigs.

In man, the effects of steroids on the lymphoid system in vivo were dramatically shown by Caffey and Silbey.[30] In their study, infants given 1.0 to 2.5 mg per kilogram per day of oral prednisone or triamcinolone for seven days showed a 19 to 44 per cent decrease in the size of the thymic shadow. After steroids were stopped, the thymic shadow resumed its original size, sometimes after a temporary "overshoot." Regarding peripheral lymphoid tissues, lymphopenia has been described in normal man after steroid therapy,[3] but it is not easy to achieve and does not always occur. A single massive dose of 1000 mg of prednisolone given intravenously did lower the peripheral lymphocyte count by 74 per cent in four hours.[11] It should be noted, however, that the infusion contained sufficient preservatives (including 250 mg of phenol) to produce systemic symptoms, and the possible relation between these substances and the leukopenia is not clear. After this massive dose, total plasma steroids rose from 0.1 μg per milliliter to a peak of 10 to 15 μg per milliliter at one hour and had fallen to 1 μg per milliliter by eight hours. Thus, the plasma bathed cells in concentrations of prednisolone of approximately 3×10^{-3} to 3×10^{-6}M for eight hours.

Human lymphoid cells are fairly resistant to steroids in vitro when compared with cells from steroid-sensitive species. Although mouse thymus cells labeled with ^{51}Cr showed appreciable isotope release (as a measure of cell death and lysis) after culture for six hours with 10^{-6} to 10^{-3}M cortisol succinate, human thymus cells cultured under identical conditions did not demonstrate increased isotope release even with 10^{-3}M cortisol succinate.[31] Guinea-pig thymus cells were just as resistant as human cells. In other studies, human peripheral blood lymphocytes showed little damage when cultured with cortisol in contrast to rat lymphocytes, which were severely damaged.[23,32] Therefore, the central and peripheral lymphoid cells of steroid-resistant species are less affected by glucocorticosteroids in vivo and in vitro than the lymphoid cells of steroid-sensitive species.

Corticosteroids and Circulating-Antibody Production

Inhibition of circulating antibody production by steroids has been repeatedly shown in steroid-sensitive animals.[4,6,33] For example, steroids produced a diminution in the hemolysin response to foreign erythrocytes in rats[34] and in mice in most experiments.[35-37] Male (but not female) rats treated with prednisolone showed a decreased production of antibodies to typhoid H antigen.[37] Cortisone-treated rabbits had decreased titers of antibodies to a number of protein antigens.[10,38,39] Administration of cortisone (2.5 to 5.0 mg per day) inhibited antibody production whether the hormone was given early or late in the antibody response.[33]

Circulating-antibody responses are correspondingly more difficult to inhibit in steroid-resistant species. In guinea pigs, the precipitating-antibody response to egg albumin in adjuvant was 75 per cent suppressed only by an intensive regimen of cortisone acetate.[40] Monkeys showed no change in secondary responses to tetanus toxoid.[14] In man, there are virtually no conclusive data indicating that steroids inhibit the production of circulating antibody.[41]

Corticosteroids and Cell-Mediated Immunity

In steroid-sensitive species, there has been relatively little study of classic manifestations of cell-mediated immunity such as tuberculin-type reactions and contact dermatitis. Glucocorticosteroids have been shown to inhibit skin allograft rejection in mice, however, at a dose of 0.4 mg cortisone acetate per day (equivalent to about 20 mg per kilogram of body weight).[42] These agents also potentiate the effects of antilymphocyte serum in prolonging skin-graft survival.[42a] Doses in the same range had similar effects in hamsters[43] and rabbits.[44]

In the guinea pig, by contrast, an equivalent dose produced no prolonged survival of skin grafts, whereas five times more steroids did have some effect.[45] The guinea pig has also been extensively used for the study of tuberculin sensitivity and con-

tact dermatitis, and in some cases the effects of steroids on these reactions have been studied. If the animals were sensitized with live tubercle bacilli, 1 to 10 mg of cortisone acetate (or its equivalent) given daily had little or no effect on tuberculin testing.[46-48] In a passive-transfer experiment using peritoneal exudate cells from donors sensitized with tubercle bacilli, cortisone acetate was ineffective in suppressing the tuberculin reaction if given either to the donors or to the recipients.[49] Guinea pigs sensitized with tubercle bacilli in the form of Freund's complete adjuvant, however, did show a suppression of the tuberculin test if cortisone acetate was given at a dosage of 5 to 10 mg per day for 30 days.[49] This protocol includes a less potent form of sensitization and greater doses of steroids over a longer time than do the previous experiments. In guinea pigs made contact sensitive to 2,4-dinitrochlorobenzene, cortisone acetate (30 mg per day) given during sensitization or just before skin testing did not cause an inhibition of the skin test.[50] In passive-transfer experiments using the same sensitivity system, cortisone treatment of the recipients was without effect, whereas treatment of the donor had moderate inhibitory effects.[51]

In man, it was shown soon after steroids became available that they would inhibit a positive tuberculin test if given orally[52] or if injected into the site of the test.[53] A more recent study using repeated PPD tests (5 TU) showed that after prednisone (40 mg per day orally) was started, an average of 13.6 days was required to convert the tuberculin tests from positive to negative.[54]

The above data indicate that in steroid-resistant species, glucocorticosteroids can suppress manifestations of cell-mediated immunity, but that large doses or prolonged treatment are required to do so.

Heterogeneity of Lymphoid Cells

The above survey indicates that there is a species heterogeneity in the response of lymphoid cells and immunologic reactions to glucocorticosteroids. Recent research in cellular immunology has shown a remarkable heterogeneity within the lymphoid cell compartment even in a given species. This subject is now the center of very active research and recently has been extensively reviewed in this journal by Graddock, Longmire and McMillan.[55] The reader should consult these articles for a fuller understanding of the subject, and the following description is merely a summary that is essential to the subsequent discussion.

There are two "primary" lymphocyte-producing organs in the adult mammal, the thymus and the bone marrow. The thymus cortex produces small lymphocytes at a rapid rate. As these cells move inward to the thymic medulla, they mature and also divide more slowly. Lymphocytes appear to leave the medulla to enter a recirculating pool of relatively mature long lived lymphocytes. The path of recirculation includes the blood, the "thymus-dependent" areas of the spleen and lymph nodes, the lymphatics and the thoracic duct (perhaps in small degree the bone marrow), but the thymus itself is not part of the main recirculation pathway. Heterogeneity within the thymus and thymus-derived populations is reflected in differences not only in turnover rate and circulation but also in surface antigenic markers.[56,57] While in the thymus, these lymphocytes will be called "thymocytes." Their descendants in the peripheral lymphoid tissue will be termed "T lymphocytes."

The other arm of lymphocyte production begins in the bone marrow, where there is also a very rapid proliferation of lymphoid cells, which will be called "marrow lymphocytes." Less is known about them after they leave the marrow since surface markers for these cells have only recently been described,[58] but they and their descendants also comprise part of the peripheral lymphoid tissue, including the blood and "nonthymic dependent" areas of the spleen and lymph nodes. These bone-marrow-derived lymphocytes in peripheral tissues will be termed "B lymphocytes." Thus, the peripheral lymphoid tissues contain both thymus-derived and marrow-derived lymphocytes in various ratios and in different sites within the lymphoid masses.

These two populations of cells have different functions. T lymphocytes appear to be the cells directly concerned in cell-mediated immunity (delayed hypersensitivity reactions, graft rejection and graft-vs.-host activity) and the response to mitogens such as phytohemagglutinin (PHA). B lymphocytes are concerned with the production of humoral antibodies and include plasmacytic cells and their precursors. There is growing evidence that the cooperation of both types of cells is needed for the production of antibodies to some antigens. In these co-operative systems, the T lymphocytes act as auxiliary "helper" cells by responding in some as yet obscure way to antigenic determinants, but they do not actually secrete free antibody. After this activation by antigen, T lymphocytes interact with B lymphocytes and perhaps again with antigen. The B lymphocytes then proceed to manufacture circulating antibody.[59] Co-operating thymus-dependent and thymus-independent cells have been found in the rat.[60] The guinea pig has been found to have co-operating cells in a hapten-carrier system, but the precise origin of these cells is not known.[61] The situation in man is even less clear, but evidence from some selective immunologic deficiencies suggests that a similar situation may exist. By analogy with the mouse model, patients with congenital sex-linked hypogammaglobulinemia (Bruton) appear to be deficient in B lymphocytes and patients with congenital thymic aplasia (DiGeorge) appear to be deficient in T lymphocytes. With this general scheme in mind, it is pertinent to re-examine the effects of corticosteroids on various types of lymphoid cells.

Thymus Cells

In sensitive species, the tremendous thymolytic effect of steroids is not exerted randomly on all the cells of the thymus. There is a selective destruction of cells, and in morphologic terms, it is the cortex of the thymus that is sensitive to steroids whereas the medulla (which comprises less than 10 per cent of the adult-mouse cortex) is resistant.[62,63] In terms of cell turnover rates, the short-lived thymus cells are more sensitive than the long-lived cells.[64] In

terms of cell markers, steroids selectively destroy cells with the TL (thymus-leukemia) marker (a surface component present on most lymphocytes in the thymus, but undetectable on normal peripheral lymphocytes), while relatively sparing the thymic cells with the most H-2 isoantigens.[65] In comparison with cells from lymph nodes or spleen, populations of thymus cells have limited but definite capabilities in mounting immunologic reactions. These capabilities inhere in the steroid-resistant population,[62] as shown by the fact that in vivo treatment with corticosteroids destroys up to 98 per cent of the thymic cells; yet the small remnant contains the immunologic capability of the whole organ in terms of its graft-vs.-host reactivity or helper-cell activity in the response to heterologous erythrocytes.[27,66] These paradoxical results indicate that the major portion of the thymus — i.e., the cortex — contains lymphoid cells that have potential but not actual immunocompetence, and it is these not yet competent cells that are most sensitive to steroids. The fraction of thymus cells that have actual immunocompetence is small, and part of the reason for the apparent weakness of thymic-cell populations in expressing T-cell activity is that the immunocompetent cells are "diluted out" by vast numbers of immunologically incompetent thymocytes.

Experiments of this kind have not yet been done in steroid-resistant species.

Thymus-Derived Cells

If thymic medullary cells are similar to thymus-derived cells of the recirculating pool, one would expect that the latter would be relatively resistant to steroids (when compared with thymic cortical cells). Indeed, in the mouse, cells in the spleen and the bone marrow active in initiation of graft-vs.-host reactions are resistant to steroids, as are splenic helper cells active in the hemolysin response to sheep erythrocytes.[27,31] Cells active in graft rejection, delayed hypersensitivity and PHA response have not yet been evaluated. Nevertheless, it is clear that in the mouse, steroids do not greatly suppress the immunocompetent central or peripheral lymphoid cells of the thymic limb of the immune response.[67]

Activation of Thymus-Derived Cells

The previous two sections have discussed the question of whether steroids will inactivate thymocytes or T lymphocytes before their immunologic activation. A somewhat different but related question is whether steroids will inhibit the activities of lymphocytes that are triggered by specific (antigenic) or nonspecific (so-called "mitogenic") stimuli. Taken together, these events are often called lymphocyte activation.

One of the best studied examples of lymphocyte activation is that produced by the plant mitogen, PHA. Small lymphocytes cultured with PHA for several days undergo dramatic morphologic changes, including enlargement of nucleus and cytoplasm with an increase in ribosomal content. This morphologic change is often termed "blast transformation." It accompanies biochemical changes in lymphocyte metabolism characterized by an early increase in RNA and protein synthesis followed by synthesis of DNA and often mitosis. There is general agreement that stimulation by PHA is primarily a property of T lymphocytes.

Soon after these remarkable PHA-induced changes were noted, Nowell[68] found that this blast transformation of human lymphocytes was inhibited in the presence of prednisolone (0.1 to 0.6 μg per milliliter). Prednisolone is most effective in suppressing the blastogenic response to PHA if the steroid is added before or just shortly after PHA. If the cells are exposed to PHA for 10 minutes, later addition of prednisolone is ineffective.[69]

Similar studies measured the effects of steroids on the stimulation of DNA and RNA synthesis produced by PHA. There is general agreement that both RNA synthesis[70] and DNA synthesis[71-73] are blocked by steroids in the general range of 1 to 100 μg per milliliter. At lower concentrations, these effects may not be seen,[72] although some experiments have found definite inhibition of DNA and RNA synthesis by less than 0.1 μg of prednisolone phosphate per milliliter.[74] Preincubation of lymphocytes for three hours with cortisol succinate (100 μg per milliliter) followed by washing and then addition of PHA was also effective in blocking PHA stimulation of RNA synthesis.[70] Thus, although the peripheral lymphocytes of man appear in themselves to be relatively resistant to steroids, their activation by a nonspecific mitogen such as PHA is sensitive to steroids.

There are correspondingly fewer experiments testing the effects of steroids on the activation of lymphocytes by specific antigen, and virtually none using human cells. In the mouse, in vivo steroids inhibited neither the activity of graft-vs.-host-reactive cells against foreign histocompatibility antigens[75] nor the "education" of T lymphocytes to sheep erythrocytes.[32] The effects of low doses of steroids (1 μg per milliliter) on the sensitization of rat lymphoid cells that occurs during culture on foreign fibroblast monolayers has been studied.[76] It was interesting that although steroids did diminish the total number of recoverable lymphoid cells, the cells that survived were more efficient in producing cytotoxic effects on the target tissue. These experiments suggest that steroids killed immunologically irrelevant cells and that the lymphocytes mediating the cytotoxic reaction were able to become activated even in the presence of steroids. The data in this general area are sparse, but they point to an apparent contrast between the steroid resistance of activation by antigen and the steroid sensitivity of activation by mitogen.

Effector Mechanisms of Thymus-Derived Cells

After activation by antigen or mitogen, T lymphocytes can affect other cells either via direct cell contact or through the production of soluble mediators. The influence of steroids on these changes has been studied in a few cases. The cytotoxicity of sensitized mouse spleen cells for homologous target cells was inhibited in the presence of 25 to 150 μg per milliliter of cortisol,[77] and smaller doses of ste-

roid also inhibited the cytotoxic effects of rat lymphocytes on mouse target cells.[76] Peripheral blood leukocytes from human subjects sensitized by skin allografts were specifically cytotoxic for fibroblasts from the skin donor, but this cytotoxicity was inhibited in the presence of methylprednisolone (100 to 300 μg per milliliter).[78] Human activated lymphoid cells were also inhibited by steroids from releasing lymphotoxin, a soluble factor implicated in cell-mediated immune responses.[79] In guinea pigs, however, the release of a skin-reactive factor from lymph-node cells was not inhibited by steroids.[80] Thus, the entire picture is not clear, and it should be emphasized that in such systems, it is difficult to distinguish between the possible action of steroids in mitigating the "aggressiveness" of sensitized T lymphocytes and a protective or stabilizing effect of steroids on the target cells that are used as indicators of cell-mediated responses. The net result of the presence of steroids in either case, however, would be a diminution of the intensity of the effect.

Bone Marrow and Marrow-Derived Cells and Their Activation

In the marrow, cells with the morphologic or functional characteristics of lymphocytes are resistant to short but high dosage regimens of steroids in the mouse,[81] but longer treatment periods have been reported to inhibit these cells,[82,83] suggesting that marrow lymphocytes in steroid-sensitive species may be resistant to steroids but their precursors may be sensitive. In guinea pigs, in contrast, seven daily injections of steroids produced no change in the absolute lymphocyte count in the marrow.[84]

It is paradoxical that although lymphocytes in the mouse marrow are resistant to steroids, their descendants, the B lymphocytes in the spleen, are sensitive to steroids before exposure to antigen.[37] Since steroids are most effective in suppressing the hemolysin response to sheep erythrocytes if given *early*,[85] once B lymphocytes are activated (by T lymphocytes and antigen), they probably become more resistant to steroids. This hypothesis is in accord with the findings that the late administration of steroids does not inhibit antibody formation in a thymus-marrow co-operative system[85] and also that plasma cells secreting antibody are very resistant to steroids.[86,87] Taken together, these data indicate that the sensitivity to steroids found in the mouse antibody-forming system lies in the peripheral undctivated B lymphocyte, the precursor of the antibody-forming cell.

Fluctuations in Corticosteroid Sensitivity

The results of the above experiments demonstrate that lymphoid cells of one lineage may be steroid sensitive or resistant, depending on their location and the stage in their life cycle. These changes, outlined in Figure 1, show an interesting alternation of steroid-sensitive and steroid-resistant phases. In the thymic limb, cortical cells (sensitive) are the precursors of medullary cells (resistant) and of peripheral T lymphocytes of the recirculating pool (resistant). The activation process may be sensitive (activation by mitogen) or not (activation by specific antigen), and the activated T lymphocytes (resistant) may have steroid-sensitive effector mechanisms such as the ability to kill cells or to manufacture and release soluble substances (e.g., lymphotoxin or migration inhibition factor).

In the bone-marrow limb, precursor cells in the marrow may be sensitive; yet they give rise to bone-marrow lymphocytes (resistant), which in turn are the antecedents of peripheral B lymphocytes (sensitive). Since these cells are steroid sensitive, it is difficult to study the effect of steroids on their activation by T lymphocytes and antigen. After such

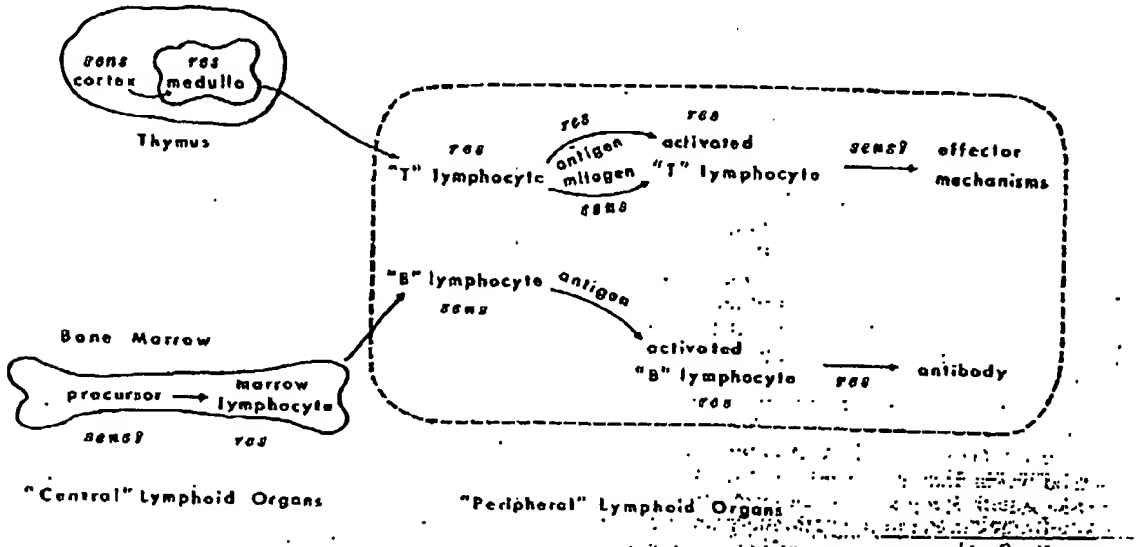

Figure 1. Schematic Representation of Sensitivity (Sens) and Resistance (Res) of Various Kinds of Lymphoid Cells and Processes.

This composite diagram includes results from steroid-sensitive and steroid-resistant species.

activation they become antibody-secreting cells (resistant).

Glucocorticosteroids and Malignant Cells

The existence of malignant lymphoid cells adds another dimension to the heterogeneity of lymphocytes. Many experiments have been done exploring the effects of steroids on cells such as mouse-ascites-lymphoma cells.[3] Firm conclusions about the sensitivity of tumors are not warranted because recent data indicate that various lines and sublines of murine lymphoma cells may vary greatly in their susceptibility to steroids.[89,90] In man, leukemic lymphocytes appear to be more sensitive to the toxic effects of steroids than normal lymphocytes or lymphocytes from patients with leukocytosis of nonmalignant origin.[91,92] The incorporation of RNA and protein precursors is also more easily inhibited by steroids in leukemic than in normal cells.[91] These studies suggest a rationale for the use of steroids in the treatment of leukemias and lymphomas, but attempts to correlate the inhibition of RNA synthesis in lymphocytes by steroids in vitro and the clinical response to steroids in leukemia in vivo have shown great variability.[92] Whether there are "T-cell leukemias" and "B-cell leukemias" in man is an intriguing but unanswered question.

Effect of Glucocorticosteroids on Cellular Metabolism

There is a very large body of data on the effects of steroids on the metabolism of lymphoid cells. Most of the experiments have used rat thymocytes because they provide a large source of relatively homogeneous lymphoid cells. From the standpoint of the above discussion, however, it should be clear that these experiments indicate only the effects of steroids on the cells of a specific organ of a steroid-sensitive species, and that in fact the lymphoid-cell population of this single organ is heterogeneous. Most of the cells in the preparation are rapidly cycling thymus cortical cells that (at least in the mouse and presumably also in the rat) are immunoincompetent. The spontaneous activities of these cells may not be analogous to the processes activated by mitogen or antigen of more mature thymus-derived cells discussed earlier. Furthermore, effects on the minority population of medullary cells will be difficult if not impossible to see because of the biologic "noise" produced by the large number of cortical cells.

With these considerations in mind, the effects of steroids on the spontaneous metabolism of rat thymus cells can be summarized. Many studies have shown that thymus cells from rats given steroids in vivo have decreased capabilities for synthesizing nucleic acids when the surviving thymus cells are removed from the animal and studied in vitro.[93,94] RNA has been most extensively examined, and there is evidence that RNA polymerase activity is impaired[95,96] and amino acid incorporation is decreased.[97,98] These studies all raise the question of whether steroid treatment in vivo merely damages cells performing these functions at a high rate, leaving for study the relatively unscathed minority of cells that metabolize more slowly. Similar findings have been made when the cells were exposed to steroids in vitro.[97,99,100] There is now considerable controversy over the question of whether these effects of steroids on nucleic acid and protein metabolism may reflect changes in earlier stages of cellular metabolism.[100-102] Inhibitory effects of steroids require glucose in the medium,[99] and evidence exists that glucose uptake is impaired by steroids,[103] but there is disagreement about whether this effect disappears in anaerobic environments.[101,104] It is interesting that in 1966, Trowell noticed that rat lymphoid cells treated in vitro with cortisone had morphologic changes similar to those produced by glucose deprivation (and by x-rays). He suggested that inhibition of uptake or metabolism of glucose was a common basis for the effects of cortisone, x-rays, mitotic poisons and barbiturates.[35]

As expected, similar findings have been reported for rabbit thymus[105] and lymph-node cells.[106] In the latter case, Kidson believed that since decreased RNA synthesis could be found as early as five minutes after exposure to cortisol succinate (5 μg per milliliter), it represented the first effect of steroids.

Human cells have been far less widely studied. In the following reports, investigators have used peripheral blood lymphocytes, a relatively long-lived population of mature cells, probably at least half thymus derived, and in many ways at the other end of the lymphocyte spectrum from thymus cortical cells. Steroids did not inhibit basal RNA synthesis in these cells, but did inhibit PHA-stimulated RNA synthesis.[70] Basal amino acid incorporation was depressed,[107] and both basal and PHA-induced glucose uptakes were curtailed by culture in the presence of steroids.[108,109] Although these findings are similar to those observed with use of thymus cells, it is clear that a considerable amount of information in this area is needed. It is quite likely that the effects of steroids will be interwoven with actions of catecholamines and cyclic AMP in lymphocytes as they already have been in muscle.[110]

Glucocorticosteroid Receptors

There is now evidence that steroids can be taken up by lymphoid cells by two mechanisms; one shows low-affinity, temperature-independent, noncompetitive kinetics, and the other shows high-affinity, temperature-dependent, steroid-competitive kinetics compatible with the existence of receptors specific for steroids.[111] There is controversy over whether specific binding occurs almost exclusively in the nucleus[112,113] or in both nucleus and cytoplasm.[88] An exciting recent finding has been made during the in vitro study of mouse-lymphoma cell lines and their variants. Some cell lines were easily killed by cortisol (3×10^{-8}M) whereas others were much more resistant, and the sensitive lines bound more cortisol in cytoplasm and nucleus than the resistant cells.[88] This raises the possibility of studying species differences and lymphoid heterogeneity within species in terms of specific steroid binding. In another cell system, Baxter and Tomkins have been able to correlate the degree of steroid binding with the activities of various steroids in inducing

tyrosine aminotransferase in hepatoma cells.[114] The problem has recently been reviewed.[114a]

Summary of Actions of Glucocorticosteroids on Lymphoid Cells

There is no doubt that lymphoid cells are sensitive to glucocorticosteroids, but the material presented above indicates that several mechanisms (Table 3) may exist and that different lymphocyte populations are affected differently.

Table 3. Possible Mechanisms of Glucocorticosteroid Action on Lymphoid Cells.

1. Lymphocyte destruction:
a) Sensitive species—thymus cortex, some peripheral marrow-derived cells, some leukemic cells
b) Resistant species—few if any normal cells, some leukemic cells
2. Inhibition of cellular metabolism & activation:
Sensitive & resistant species—basal metabolism and some kinds of activation of cells of thymic & bone-marrow derivation, some leukemic cells
3. Redistribution of lymphocytes:
Some thymus-derived cells in mice

Destruction of Lymphocytes

In steroid-sensitive species, lymphocytes are destroyed in the thymus cortex, and also, probably, some peripheral marrow-derived cells. These animals, however, also contain other subclasses of lymphoid cells that are not destroyed by steroids, and these subclasses include many of the immunocompetent cells of the peripheral tissues, particularly T lymphocytes (Fig. 1). In steroid-resistant species, there is little evidence that pharmacologic doses of steroids cause any great degree of destruction of normal lymphocytes in vivo. Leukemic lymphocytes may be destroyed if one considers the rapid fall in lymphocyte count and the rise in serum uric acid that may occur during steroid treatment of leukemia. It is tempting to speculate that direct lysis by steroids may be a characteristic not of inactive but of more rapidly metabolizing or dividing lymphoid cells. The steroid resistance of bone-marrow lymphocytes that are probably dividing rapidly does not fit this concept, however.

Inhibition of Cellular Metabolism

Effects in this general area have been described in both steroid-sensitive and steroid-resistant species at various levels of cellular metabolism from glucose uptake and nucleic acid synthesis to cytotoxic activities. Such inhibition has been seen both in "resting" lymphocytes with low rates of metabolism and in the same cells after activation by nonspecific mitogens. The lack of effect of steroids on specific antigen activation remains unexplained, but since this response involves far fewer cells than mitogen activation does, inhibitory effects may be more difficult to see. It is likely that this kind of inhibition is the major mechanism of steroid-action on lymphoid cells in man. Even the rapid shrinkage of the human thymus in vivo[30] can be easily understood in terms of inhibition of thymus-cell metabolism in the absence of direct cytolysis. The normal human infantile thymus has a very high rate of cell division. Any agent that greatly impedes this cell proliferation (without changing the intrathymic death of cells) would cause a shrinkage of the organ. When the agent was removed, one would expect the organ to increase in size as the uninhibited dividing cell compartment expanded.

Redistribution of Lymphocytes

The redistribution of lymphocytes between various compartments of the body is another possible mechanism of action of steroids, but one that has received little attention. Agents that change the distribution or traffic of lymphoid cells are already recognized — e.g., enzymes[115] and pertussis vaccine.[116] Steroids have effects on nonlymphoid cells, and the eosinopenia that follows cortisol administration in rats has been interpreted to result from sequestration of eosinophils in areas other than the blood.[117] Steroids also decrease the number of mononuclear phagocytes in the blood of mice by inhibiting the promonocytes in the bone marrow and perhaps also by sequestering some existing monocytes in the peripheral tissues.[118] The effects of steroids on the traffic of lymphocytes has been studied in guinea pigs, in which they have been shown to increase the export of cells from the thymus[119] and from the spleen.[120] Recent experiments in mice show that cortisol treatment *increases* the T-cell population in the bone marrow and that at least some of these T cells come from the spleen.[121,122] No data are available in man.

Steroid Effects on Other Aspects of Immunologic and Inflammatory Processes

Corticosteroids influence a wide variety of processes involving inflammation, immunologic response, handling of infectious agents, etc. After over 20 years of study, there is considerable disagreement about how steroids work in these areas. Inflammatory processes are complex and in themselves heterogeneous. A variety of cellular and humoral agents take part, and because steroids produce changes in such basic cellular processes of lymphocytes as nucleic acid synthesis and energy metabolism, it is not surprising that they have been found to affect cells and processes not of the lymphoid system. This subject is outside the scope of this report, and various reviews have appeared.[4,123] The following processes have recently been shown to be *inhibited by steroids*: release of monocytes into the blood (mice)[119]; spreading on glass by macrophages (mice)[124]; chemotaxis of neutrophils (guinea pigs)[125]; movement of antigen-antibody complexes across a basement membrane (rabbits)[126]; and release of active kinins from substrates (man)[127]. Also, it is important to recognize that these processes are in fact inter-related and have to be studied in intact as well as in isolated systems. For example, the cortisone-induced depression in macrophage accumulation may be caused not primarily by effects on the macrophage but by the inactivation of lymphoid cells that is a likely prerequisite of macrophage accumulation.[128] The relative importance of these various

direct and indirect activities of steroids awaits further investigation.

Conclusions

Glucocorticosteroids affect lymphoid cells and tissues in many ways. There are marked species differences in these responses. The mouse, rat, hamster and rabbit are steroid sensitive; many of their lymphoid cells are easily lysed by steroids, and in these species steroids inhibit antibody

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : C. Carling, et al.

Serial No. : 08/317,407

Filed : October 3, 1994

For : COMBINATION OF A BRONCHODILATOR AND STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS, AS WELL AS ITS USE AND THE PREPARATION THEREOF

DECLARATION UNDER 37 C.F.R. § 1.132

I, Jan William Trofast, Ph.D., declare as follows:

I am Principal Research Scientist in Pharmaceutical and Analytical Research and Development at Astra Draco AB in Lund, Sweden, a subsidiary of Astra AB, the assignee of the above-identified application. My curriculum vitae is attached as Exhibit A.

I am a coinventor of the subject matter of the above-identified patent application, and I participated in the August 17, 1994 Examiner interview. I am familiar with the office actions issued during the course of prosecution of this application and its parent, as well as the prior art patents of Brattsand, et al. and Murakami, et al. cited against the pending claims. The pharmacological *in vivo*

studies set forth below were carried out at my behest by pharmacologists at Astra Draco AB.

The tests were performed to determine the effect of a fixed combination of budesonide and formoterol on the inhibition of lung inflammation. The test model employed was the Sephadex-induced edema model. The model is well established in the field and widely recognized as universally predictive of anti-inflammatory properties, as attested to by a number of published articles. Three representative articles (Källström, et al., Agents and Actions 17, 355-357 (1985); Kubin, et al., Int. Arch. Allergy Immunol. 98, 266-272 (1992) and Brattsand, et al., Int. J. Microcirc. Clin. Exp. 5, 263 (1986)) are attached hereto as Exhibit B.

Sephadex was administered intratracheally to Sprague-Dawley rats together with saline (first control), budesonide, formoterol, or budesonide-formoterol combinations in various budesonide-formoterol concentration ratios. Either six or twelve animals were subjected to each experimental regimen as indicated in Table I below. The animals were sacrificed the following day, their lungs excised and the inflammatory process measured as lung weight increase due to edema.

The weight increase of lungs removed from animals subjected to the Sephadex-saline regimen compared to the weight of lungs removed from a second group of control animals, to which only saline (i.e., neither Sephadex nor any test compound) was administered, was taken as representative of maximum Sephadex-induced edema. Inhibition of the Sephadex-induced lung edema by a test substance was determined as per cent reduction of induced edema in the presence of the test compound compared to the maximum edema induced in the Sephadex-saline controls. The results are presented in Table I below:

TABLE I

Inhibition of Sephadex-Induced Lung Inflammation in Rats

Compound	Amount Administered (nmol/kg)	n†	% inhibition
1. Formoterol	5	6	21.0
2. Budesonide	5	6	3.1
3. Formoterol + Budesonide (1:1)	5 + 5	6	42.1
4. Formoterol	2	12	13
5. Budesonide	10	12	-14
6. Formoterol + Budesonide (1:5)	2 + 10	12	28*
7. Budesonide	20	12	-9
8. Formoterol + Budesonide (1:10)	2 + 20	12	52**
9. Budesonide	40	12	9
10. Formoterol + Budesonide (1:20)	2 + 40	12	66**

† number of animals subjected to regimen

Statistical parameters: * $p<0.05$; ** $p<0.01$

Comparison with Sephadex-induced inflammation in control animals showed that neither budesonide (at any of the four administered concentrations) without formoterol nor formoterol (at either of the two administered concentrations) without budesonide significantly inhibited the induced edema, based on the criterion of the Wilcoxon rank sum test. Furthermore, even the sum of the individual

effects would not be considered significant by this criterion.

By comparison, several fixed molar ratios of formoterol to budesonide given in combination (1:5 ratio, 28% inhibition; 1:10 ratio, 52% inhibition; 1:20 ratio, 66% inhibition) showed significant reduction of lung edema in the Sephadex model as judged by the criterion of the Wilcoxon rank sum test. In these tests performed with formoterol-budesonide combinations, the statistical analysis was obtained by comparing the effect of a given combination with the effect of the corresponding amount of budesonide administered without formoterol. This type of analysis was designed to particularly point up enhanced anti-inflammatory effects of the combination in comparison to the effects expected (and observed) for the anti-inflammatory steroid (budesonide) component alone.

None of the values observed, whether positive or negative, for inhibition of Sephadex-induced inflammation by budesonide alone are statistically significant. All such values simply demonstrate that budesonide at the concentrations administered is ineffective in reducing inflammation. This is in keeping with what would be predicted from the known pharmacology of budesonide; concentrations of the steroid in the range from 5 nmol/kg

to 40 nmol/kg, as in the tests described herein, would not be expected to demonstrate significant anti-inflammatory effect in rats. However, as the data of Table I show, budesonide-formoterol combinations provided significant reduction of inflammation, even though the concentration of budesonide administered remained in the 5-40 nmol/kg range.

It is known in the pharmacology art that rat cells exhibit 3-10 times greater sensitivity to glucocorticosteroids than does man, although this could differ to some extent in *in vivo* test models. The administration of a 1:1 molar ratio of formoterol to budesonide in the test regimen is reflective of this expected greater sensitivity in the rat. It can be seen from the test data (obtained from 6 test animals for each experimental condition) on line 3 of Table I that budesonide and formoterol administered together at this molar ratio are also highly effective (42.1% inhibition) in reducing Sephadex-induced lung edema.

The administered 1:5, 1:10 and 1:20 molar ratios of formoterol to budesonide are more reflective of the types of ratios that one of skill in the art would envision using in humans, given the lower sensitivity of man to the budesonide component. As pointed out above, these ratios,

in testing in a larger number of animals, were seen to be highly effective in reducing lung inflammation.

The data demonstrate that budesonide-formoterol combinations over a range of molar ratios provide an enhancement of anti-inflammatory effect which, unexpectedly, is significantly greater than the sum of the individual anti-inflammatory effects of the two active agents. More precisely, neither budesonide without formoterol nor formoterol without budesonide provided significant reduction of Sephadex-induced inflammation at the administered concentrations, whereas treatment of animals with the combined agents in the same concentrations administered individually resulted in significant reduction of inflammation. The unexpected effects were seen for combinations more appropriate for the known pharmacology of the active agents in rats, as well as for combinations more appropriate for known human pharmacology.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements were made with the knowledge

that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: dated 24 May 1995

JAN W. TROFAST, Ph.D.

EXHIBIT A

(4 Pages)

ASTRA
ASTRA DRACO

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Lund, September 19, 1994

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EXHIBIT B

(10 Pages)

M-190

SEPHADEX-INDUCED INFLAMMATION IN RAT LUNG.
I. MODEL DESCRIPTION AND PROTECTIVE ACTION BY DRUGS.

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Inflammation and edema have pathophysiologic importance in several bronchial and alveolar diseases. Rather few small animal models have been described allowing the testing of anti-inflammatory action of intratracheally instilled (i.t.i) or inhaled drugs on these conditions. A new model has been developed, based on i.t.i. Sephadex beads (5 mg/kg). The beads provoke bronchial and pulmonary inflammation by a combination of allergic and immunologic mechanisms. Sephadex consists of dextran, to which rats have an endogenous hypersensitivity. Besides, the particular form probably triggers inflammation also via other immunologic mechanisms. Intrapulmonary pressure (measured according to Konzett-Rössler) and wet lung weight rise only slightly for the first hours, while there is a great rise during the interval 7-20 h. This rise is ascribed to the simultaneous development of a profound interstitial lung edema. As studied by bronchoalveolar lavage there is a marked infiltration into airways of neutrophils (from 3 h and onwards), of eosinophils (from 7 h) and later also of monocytes and lymphocytes.

Based on the gain of lung weight 20 h after Sephadex instillation, the anti-inflammatory activity of different types of drugs has been studied. Drugs known to reduce enhanced vascular permeability (e.g. the GCS budesonide and the β_2-stimulant terbutaline) can effectively block the edema. The NSAID indomethacin has no protective action. A high dose of diethylmaleate (a known deplctor of glutathione) effectively inhibits the edema. The efficacy of GCS and of diethylmaleate, but the the lack of efficacy of indomethacin would together suggest that glutathione-containing leukotrienes are important inflammatory mediators. The edema can also be blocked by scavengers such as catalase, DMSO and DMTU, which suggests that hydrogen peroxide and some types of oxygen radicals contribute. However, SOD and iron chelators have no anti-edema efficacy.

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SEPHADEX-INDUCED INFLAMMATION IN RAT LUNG II. LIGHT AND ELECTRON MICROSCOPIC STUDIES.

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The major reason to that animal models of disease are developed is to reproduce human disorders in order to study the pathogenesis and pathophysiology of the process. The optimal hypersensitivity model would show similar picture of human disease and allow to study individual components of the hypersensitivity response. In abstract I a rat model of lung inflammation is described, where intratracheal instillation of Sephadex beads leads to an inflammation in the respiratory airways and alveolitis. The inflammation is probably induced partly by allergic mechanisms, as the Sephadex bead consists of dextran to which rats have an endogenous hypersensitivity. Pulmonary tissue specimens were examined by light and electron microscopy after 15 min., 2,4, 7 and 24 hours and after two weeks of Sephadex or NaCl instillation. Microscopically an immediate response was seen at 15 min. as a widespread perivescular edema, probably due to increased venuler permeability. Endothelial cells were swollen. Later a mixed celluler infiltration with a prominant eosinophlie was noted, mainly around the respiratory airways. Respiratory airways mucose showed an asthma-like reaction with smooth muscle contraction, edema, infiltration of inflammatory cells with a striking increase in eosinophils. Sloughing of the epitelial lining cells and mucosa desquamation was observered. Mast cells in various stages of degranulation were seen between bronchial epithelial cells. Most of the Sephadex beads were spread rapidly in both alveolar and subpleural tissue. Around the beads there was a heavy granulomatous reaction, which could be noted in all specimens. Granulomas were mainly composed of monocytes and eosinophil cells with some giant cells of foreign body type. The inflammatory reaction was most prominent after 24 hours. All changes were resolved after two weeks. Owing to the particulate form of the Sephadex beads general immunologic mechanism may contribute to a granulomatous reaction. Sephadex induced reaction of the lung tissue is suitable as a model for study of: 1. Interstitial edema. 2. Asthma-like reaction on airway mucosa and 3. Granulomatous alveolitis.

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A rat model for testing anti-inflammatory action in lung and the effect of glucocorticosteroids (GCS) in this model

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It has been observed in patient studies that a better differentiation between antiasthmatic action in the lung and inhibition of adrenal function is reached by inhaled GCS (e.g. budesonide BUD) than that attained by oral GCS [1]. The reasons for the better differentiation reached by inhaled GCS are not known. One proposed but still unproved reason is that inhaled GCS act by local (topical) activity on airway mucosa and lung microvasculature, before they are absorbed and 'diluted' in the systemic circulation. The aim of the present study was to create a GCS sensitive airway inflammation in a rat model and to study the importance of the route of GCS administration for the

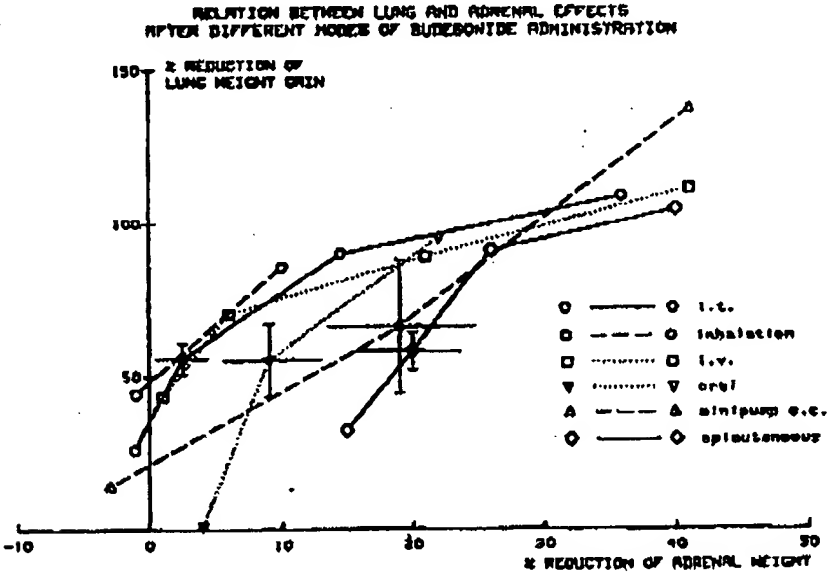

Figure 1
Relation between the reducing effects on lung edema formation and the adrenal weight, as influenced by the route of BUD administration. i.t. = intratracheal instillation, inhal. = inhalation, i.v. = intravenous injection, oral = oral administration, minipump s.c. = continuous release from s.c. implanted minipumps (Alzet®), epicutaneous = topically applied on a shaved area on the back skin. For doses inhibiting the lung edema formation by about 50% the s.e.m. are outlined. $N = \geq 6$ rats per dose level.

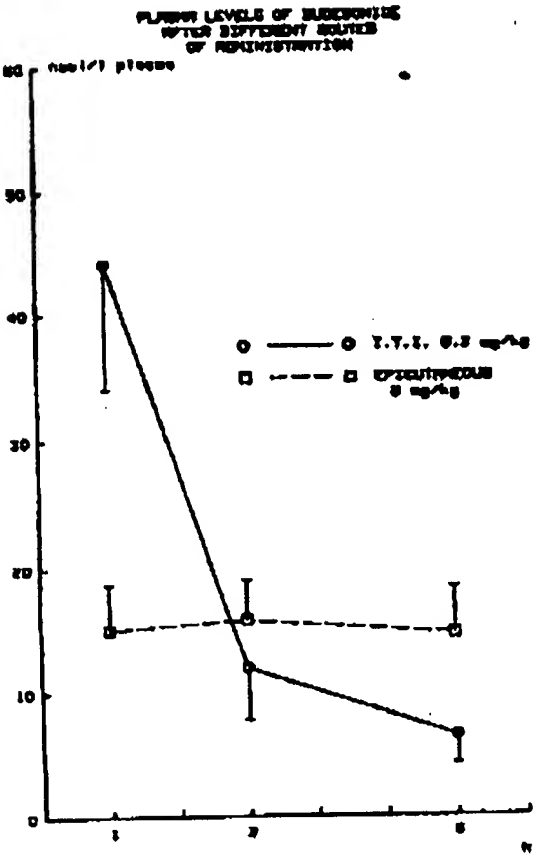

Figure 2
Plasma levels of BUD after i.t. instillation, 0.3 mg/kg, or epicutaneous application, 3 mg/kg. Mean ± s.e.m. of 5 rats.

relationship between anti-inflammatory action in lung and inhibition of hypothalamus-pituitary-adrenal axis.

Bronchiolitis and alveolitis were induced in male SD rats (220 g) by intratracheal (i.t.) instillation of Sephadex beads (5 mg/kg). Sephadex consists of dextran to which rats have an endogenous hypersensitivity [2]. There is no immediate reaction, but after some hours the beads attract neutrophils, eosinophils and macrophages. These form cuffs around the beads, which are situated for the first hours in bronchioles and later on also more peripherally. The histological picture is a focal bronchiolitis and alveolitis leading to a peribronchial and interstitial edema and to impaired ventilation. These pathological changes can be quantified by the gain of lung wet weight, the rise in which correlates in time with the infiltration of granulocytes (esp. of eosinophils) and with the impaired ventilation. After one day the lung weight increases by 50–75%, the weight gain persisting for at least 4 days.

BUD given by i.t. instillation 30 min before Sephadex counteracted partly (dose 0.1 mg/kg) or nearly completely (dose 1 mg/kg) the wet lung weight gain, impaired respiration, histological changes and influx of eosinophils [3]. To study if the protection induced by i.t. instillation depends on a local action, a refined model was used in which only the left lung lobe was pretreated with instilled BUD while Sephadex was given to both lung halves. The consistent result of such tests has been that the same protection against edema was obtained in the right as in the locally treated left lung lobe. This demonstrates that the anti-edema efficacy of i.t. instilled BUD does not rest on a local action at the application site in lung.

To be able to study adverse effects on adrenal function Sephadex-treated rats were given BUD twice a day for four days. At sacrifice the gain in wet lung weight and the adrenal weight were determined. Six routes of BUD administration were tested and the results are given in Fig. 1. When BUD was given by i.t. instillation, inhalation or i.v. injection, it was possible to inhibit the lung edema formation by up to 50% without reducing the adrenal weight. Such a differentiation between lung and adrenal effects was not attained with three other routes tested (Fig. 1). Diminished lung edema formation by 50% was then coupled to reduction of the adrenal weight by ~10% (after oral administration) or by ~20% (after epicutaneous or continuous from s.c. minipumps). Thus, the route of BUD application affected the relationship between lung and adrenal effects markedly but there was no simple correlation between selective lung action and the local mode of application to the lung.

The levels of circulating BUD in plasma were determined after 3 routes of administration: i.t. and i.v. representing routes differentiating between lung and adrenal effects and epicutaneous as a route without such separation. Doses with about the same anti-edema efficacy in lung were selected (i.t. and i.v. 0.3–0.4 mg/kg and epicutaneously a dose about ten times higher). BUD was determined with a RIA method [4]. I.v. and i.t. administration gave rather similar plasma levels from 3 minutes onwards, but the i.v. values were higher for the first 2 minutes. After i.t. instillation the plasma levels of BUD were ~2000 after 1 minute, after 1 h ~40, after 3 h ~10 and after 6 h ~6 nmol/l. Epicutaneous administration gave no clear plasma peak, and the levels were stable at ~15 nmol/l between 1 and 6 hours. Figure 2 shows one experiment comparing the BUD levels in plasma after i.t. and epicutaneous application. At 1 h the epicutaneous levels were 3 times lower than the i.t. ones ($p < 0.05$), while at 6 h the opposite relation between the two application routes was noted.

The profile demonstrated by i.t. instilled or by inhaled BUD, marked anti-edema action in lung but low activity on adrenal weight, supports the relevance of the rat model, as inhaled BUD gives a principally similar differentiation in asthmatic patients. As studied in the rat model, the following proposals can be raised currently as reasons for lung selectivity reached by i.t. instillation:

—it seems not to depend on a local action of BUD at the application site in lung;

—analyses of BUD in plasma show that i.t. instillation leads to a very rapid systemic absorption of BUD. The plasma peak following i.t. administration is seen at ~1 minute, after which time the plasma levels drop rapidly. Epicutaneous administration leads to lower but more protracted BUD levels. It is suggested that these different types of plasma curves can explain why the former but not the latter administration route differentiates between lung and adrenal activity. If so, a rather short plasma peak of BUD is

sufficient to trigger an anti-edema effect in the lung, possibly by induction of proteins with anti-inflammatory action [5]. Recent studies in our lab in the hamster cheek pouch model show that as large anti-edema efficacy can be reached by BUD given i.v. as by local application of BUD to the cheek pouch for 5 to 60 minutes [6]. The effectiveness of local application for only 5 min may suggest that BUD exerts its effect locally via endothelial cells in the exposed microvasculature. For induction of the principles inhibiting the hypothalamus-pituitary-adrenal axis, the duration of circulating BUD may be more important than the height of the peak.

An alternative explanation for the differentiation may be that the distribution of BUD between lung and brain tissue (the adrenal involution starts probably at the brain level) varies with the height of plasma levels, so that high and short peak levels would favour binding to lung tissue while prolonged plasma levels may lead to relative enrichment in brain.

Further experimental investigations are required to critically evaluate these two hypotheses.

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Original Paper

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Intratracheal Application of Sephadex in Rats Leads to Massive Pulmonary Eosinophilia without Bronchial Hyperreactivity to Acetylcholine

Key Words
Bronchial hyperreactivity
Pulmonary eosinophilia
Asthma
Sephadex
Animal model

Abstract
Fourteen Brown-Norway rats were pretreated with physiological saline (n = 7) or 500 µg Sephadex (n = 7) intratracheally. 24 h later, a bronchial provocation test was performed under pentobarbital anaesthesia using increasing doses of acetylcholine aerosol and the degree of bronchospasm was measured using a modified Konzett-Rössler method. Subsequently, leucocyte counts were determined in the bronchoalveolar lavage fluid (BALF), BALF cells were differentiated, and the chemiluminescence of the BALF leucocytes were measured. Finally, the lungs were removed and histologically examined. The cell count in the BALF was significantly ($p < 0.05$) increased in the animals pretreated with Sephadex compared to those in the saline group (mean value ± SEM: 0.38 ± 0.07 vs. 0.15 ± 0.02 × 10^6/ml). This difference was also reflected in the chemiluminescence measurements (2.51 ± 0.53 vs. 0.20 ± 0.03 × 10^6 counts/0.5 ml). In the Sephadex-treated animals there was also a significant increase in the absolute number of neutrophil (0.040 ± 0.010 vs. 0.011 ± 0.002 × 10^6/ml) and, in particular, eosinophil granulocytes (0.188 ± 0.055 vs. 0.003 ± 0.001 × 10^6/ml) in the total leucocytes of the BALF. Lung histology showed massive perialveolar and peribronchial oedema and granulomatous infiltrates, primarily with eosinophils, after intratracheal application of Sephadex; these findings were not observed in the saline group. None of these changes in the rats pretreated with Sephadex manifested themselves in increased bronchial reactivity to acetylcholine aerosol. It is uncertain if the Sephadex-induced increase in the eosinophil count is accompanied by an activation of this cell population, which appears to be of importance for the occurrence of bronchial hyperreactivity. It is clear from this animal model that the presence of inflammatory cells in the BALF and lung tissue of rats does not in itself result in increased reactivity of the airways.

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Introduction

Bronchial asthma is a chronic disease whose primary symptoms are reversible bronchospasms and inflammation of the airways with increased reactivity to a large number of irritants. Biopsies of the bronchial mucosa of asthmatics show characteristic histological changes: infiltration with leucocytes, in particular, with eosinophil granulocytes, oedema, epithelial desquamation, hyperplasia of the mucous glands and hypertrophy of smooth muscle [1]. These changes are also found in patients with mild, stable asthma, and a correlation between the degree of inflammation and the degree of bronchial hyperreactivity has been reported [2]. There has recently been increased discussion of whether eosinophils play a central role in the occurrence of airways hyperreactivity [3–5]. Damage of the bronchial epithelium by toxic, basic eosinophilic proteins [6] with resultant suspension in the production of a factor which relaxes the airway smooth muscle [7] has been cited as a possible pathogenetic factor. Furthermore, afferent nerve endings are exposed as a result of epithelial damage. Stimulation of these nerve endings may then lead to the release of bronchoconstricting and pro-inflammatory neuropeptides via an axon reflex [8]. As well as toxic proteins, eosinophils can also release other pro-inflammatory mediators such as leukotrienes [9] and reactive oxygen species [10]. Because of the possible pathogenetic significance of pulmonary eosinophilia in asthma, it is important that this effect is also found in an animal model for this disease. Walls and Beeson [11] were able to produce blood eosinophilia in rats by intravenous (i.v.) injection of Sephadex (cross-linked dextran) particles. In addition, there were increased numbers of eosinophils in the airways accompanied by hyperreactivity to i.v. 5-hydroxytryptamine [12, 13] and aerosols of 5-hydroxytryptamine and ovalbumin in sensitised animals [14]. Despite embolisation of the pulmonary vessels, it was not possible to reproduce this effect by i.v. injection of latex particles [15], which points to a Sephadex-specific effect for the eosinophilia, possibly as a result of the known endogenous dextran hypersensitivity of rats [16]. Inbred Brown-Norway rats appear to be a suitable rat strain for an animal model in asthma, since this strain is characterised by a high immunoglobulin E response to sensitisation to antigen and by blood eosinophilia [17, 18]. For this reason, we decided to test intratracheal application of Sephadex in Brown-Norway rats in order to determine whether a non-specific bronchial hyperreactivity to acetylcholine aerosol resulted from the expected eosinophilic inflammation.

Methods

Details of the methods have already been reported by us elsewhere [14, 19]. The most important technical details are summarised below.

Animals and Pretreatment

Male Brown-Norway rats (Charles River Wiga, USA) aged 12–14 weeks and weighing 250–300 g were non-operatively intratracheally instilled with either 100 µl physiological saline or 500 µg Sephadex-G 200 (Pharmacia, Uppsala, Sweden) in 100 µl saline via a plastic tube under short-term inhalation anaesthesia with methoxyfluran (Penthrane®, Abbott, Chicago, USA; 7 animals per group). The Sephadex suspensions used were prepared under sterile conditions 2 days before the investigations and stored at 4 °C.

Measurement of Bronchoconstriction

Twenty-four hours after pretreatment, the animals were anaesthetised with 60 mg/kg pentobarbital (Narcoren®, Rhone Merieux GmbH, Laupheim, FRG) intraperitoneally and their trachess cannulated and connected to a ventilation pump (60 strokes/min, 2–4 ml). The strength of the bronchospasm to aerosol applied via the ventilation pump (Rhema, Hofheim/Taunus, FRG) was measured as the increase in the respiratory resistance by means of an overflow-measuring unit at a constant pressure of 7 cm water column according to the method of Konzett and Rössler [20] as modified by Collier et al. [21] and Collier and James [22]. Increasing doses of acetylcholine aerosols, generated from stock solutions of 0.3, 1, 3, and 10 mg/ml saline, were each applied for 3 min using an ultrasonic nebuliser (Heyer USE 77, nebuliser power 4 ml/min, ventilator power 15 l/min, aerosol particle size 0.5–4 µm; Heyer, Bad Ems, FRG). The bronchoconstriction was measured for 10 min before application of the next higher dose. A direct effect of acetylcholine on the cell count in the bronchial lumen was ruled out in a pilot investigation in which non-pretreated animals ($n = 4$) were exposed to acetylcholine aerosol in the manner described above. Bronchoalveolar lavage (BAL) with subsequent cell counting and measurement of the chemiluminescence were then performed as laid out below. Compared with the values for a non-pretreated control group ($n = 4$) which underwent BAL without previous bronchoprovocation with acetylcholine, there was no significant difference between the parameters (data not shown).

Bronchoalveolar Lavage

Directly after measurement of brochoconstriction, the cannulated trachea was connected to a perfusor pump (Braun, Melsungen, FRG) instilling 2 ml of 1 m*M* EDTA in saline. This solution was instilled into the bronchial system 3 times for 1.5 min and then re-aspirated before the lavage fluid (BALF) was brought on ice (yield: at least 80% of the instilled volume). This procedure was repeated twice more, using 2 ml saline/EDTA solution each time.

Pathohistological Investigation

Directly after lavage, the animals lungs (including the trachea) were removed and fixed in 10% formalin. Discs of tissue about 3 mm thick were taken from each lobe and embedded at 65 °C in Paraplast® (Sherwood Medical Industries, St. Louis, USA) via an increasing alcohol series using xylene as intermedium. 4–5 µm sections were prepared from the embedded tissue discs, applied to uncoated slides, stained with haematoxylin-eosin, PAS and Giemsa and then examined by light microscopy.

Table 1. Cell count and chemiluminescence in the BALF of Brown-Norway rats

Pretreatment	Cell count/ml × 10^6	Chemiluminescence counts/min/0.5 ml × 10^6
Saline	0.15 ± 0.02	0.20 ± 0.03
Sephadex	0.38 ± 0.07	2.51 ± 0.53

Intratracheal pretreatment with saline (n = 7) or 500 µg Sephadex (n = 7) 24 h previously. Values as mean ± SEM.

Table 2. Absolute numbers (ml × 10^6) and percentage populations of various cell types in the total cell count of the BALF of Brown-Norway rats depending on intratracheal pretreatment (saline, n = 7, or 500 µg Sephadex, n = 7, 24 h previously; values as mean ± SEM)

Pretreatment	Mononuclear cells	Eosinophils	Neutrophils
Saline	0.136 ± 0.027 (91%)	0.003 ± 0.001 (2%)	0.011 ± 0.002 (7%)
Sephadex	0.154 ± 0.011 (41%)	0.188 ± 0.055 (49%)	0.040 ± 0.010 (10%)

Cell Count and Cell Differentiation

Immediately after lavage, 1 ml BALF was mixed with 9 ml isotonic diluent (Nova Celltrak, Waltham, USA) and 3 drops of haemolytic reagent (Nova Celltrak) to lyse the few erythrocytes. The cell count was performed using a Coulter Counter ZM (Coulter Electronics, Luton, UK). The differential count of the leucocytes was performed by light microscopy following centrifugation (700 rpm, Labofuge A, Heraeus, Hanau, FRG) of the BALF on a slide with subsequent staining with a modified May-Grünwald stain (Diff-Quik®, Baxter Dade AG, Düdingen, Switzerland). 400 cells were counted from each preparation.

Determination of Chemiluminescence

200 µl BALF were mixed with 100 µl BM-86 Wissler buffer (Boehringer Mannheim GmbH, Mannheim, FRG) and 100 µl Luminol 2×10^{-4} m*M* (Boehringer Mannheim GmbH), and incubated for 15 min at 37 °C. 100 µl opsonised zymosan (15 mg/ml) were then added and measurement was performed immediately with an autobiolumat LB 950 (Berthold, Wildbad, FRG) for 15 min. Opsonisation was carried out by washing 50 mg zymosan (Sigma, St. Louis, USA) suspended in 1 ml saline twice with saline and then incubating the suspension with 1 ml of a pooled rat serum for 30 min at 37 °C.

Statistics

The distribution-free Wilcoxon test (U test) for non-normal populations was used to calculate the significance of a difference between two parameters. The level of significance was set at $p < 0.05$. The correlation coefficient r was calculated to determine the degree of linear dependency of two parameters. The significance of a correlation was calculated according to Fisher's method.

Results

Table 1 shows mean values ± the standard error of the mean (SEM) for the leucocyte count and chemiluminescence of the leucocytes in the BALF for the Sephadex and saline groups. The bronchopulmonary inflammation induced by Sephadex is reflected in the more than 2-fold increase in the leucocyte count and the 25-fold increase in chemiluminescence compared to the values for the saline group. The greater degree of interindividual scatter after pretreatment with Sephadex compared to saline is clearly evident. In all cases, there was a significant difference in the parameters in the two groups at $p < 0.05$. In the Sephadex animals there was a highly significant correlation between cell count and chemiluminescence ($r = 0.95$; $p < 0.01$) which was not observed in the saline animals ($r = 0.65$, not significant). Table 2 shows the absolute numbers and the percentage of mononuclear cells (mononuclear phagocytes and lymphocytes), neutrophil and eosinophil granulocytes in the BALF cells. Intratracheal administration of Sephadex resulted in an increase in both the percentage and absolute number of eosinophils in particular and, to a lesser extent, of neutrophils. By contrast, the percentage of mononuclear cells in the BALF fell, although the absolute values also increased to a certain degree. The difference in the absolute numbers of the individual cell types between the Sephadex and the saline animals was significant for eosinophils and neutrophils, but not for the mononuclear cells.

Histological investigation of the lung preparations from Sephadex-pretreated rats revealed pronounced peribronchial and perivascular oedema with heavy accumulation of eosinophil granulocytes and few mixed cell infiltrates (fig. 1a, d). PAS-positive Sephadex particles were widely distributed in the alveolar lumina. There was a clear granulomatous reaction around the Sephadex particles (fig. 1b). The disseminated granulomas localised in the lung tissue were composed of mononuclear cells and eosinophils. In some of the granulomas, the eosinophils were arranged concentrically around the alveolar lumina. The mononuclear cells were predominantly macrophages with reniform nuclei, sparse heterochromatin and vacuolar cytoplasma. Lymphocytes were found only rarely in the granulomas. Only isolated giant cells (fig. 1c), neutrophils and mast cells were observed. The rats which had re-

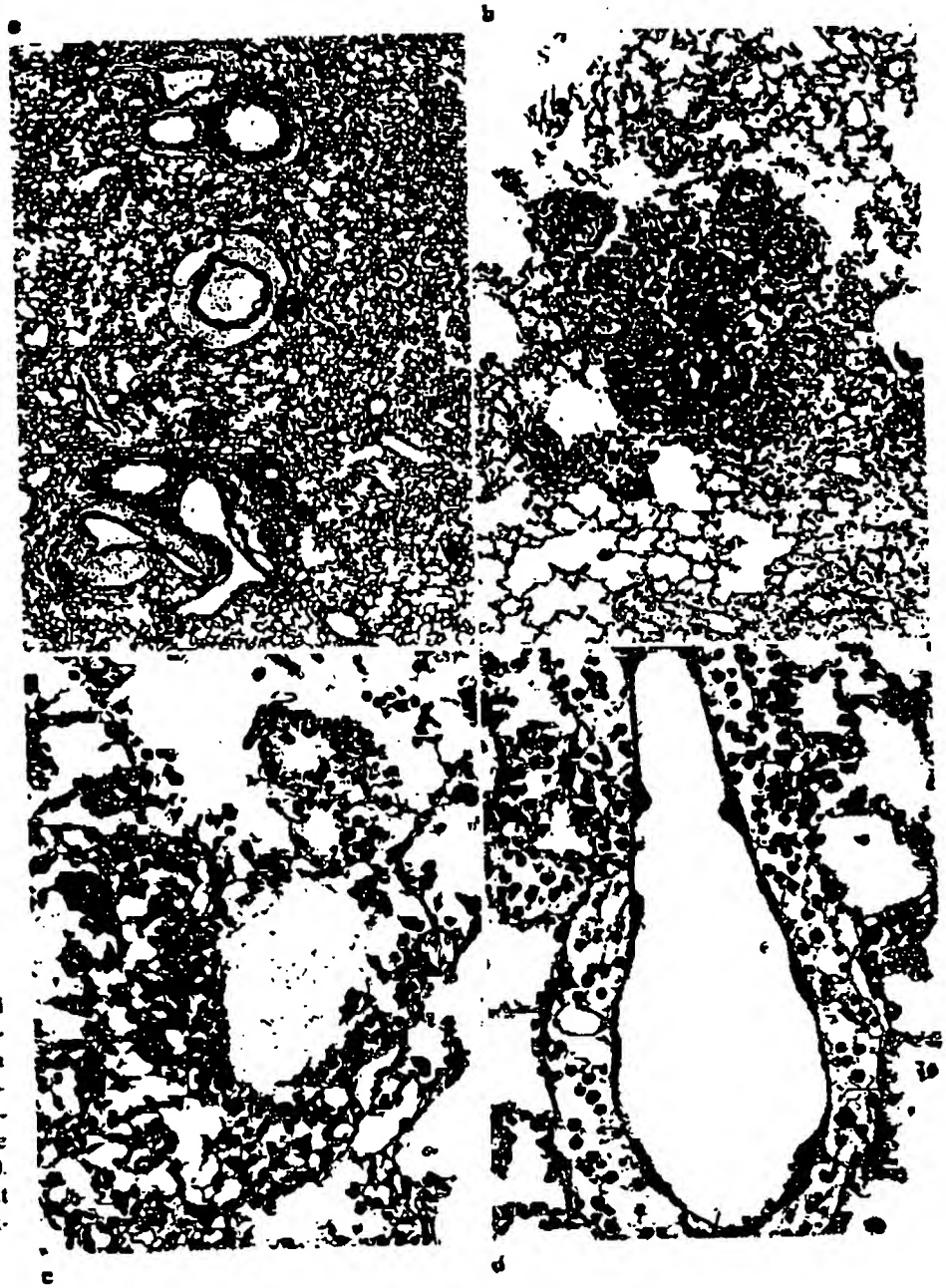

Fig. 1. Lung specimens of rats pretreated intratracheally with Sephadex 24 h previously. **a** Peribronchial/perivascular oedema and disseminated granulomatous inflammation 1:25. **b** Prominent granulomatous inflammation in the alveolar tissue around the positive PAS-stained Sephadex beads 1:100. **c** Granulomatous inflammation with a giant cell. 1:200. **d** Perivascular oedema with accumulation of eosinophils. 1:200.

ceived saline intratracheally exhibited only minimal peribronchial and perivascular oedema. Only isolated eosinophils and mononuclear cells were found in the pulmonary tissue. In spite of the massive inflammatory changes, hyperreactivity to increasing doses of acetylcholine aerosol (0.3, 1, 3, 10 mg/ml saline) was not found in Brown-Norway rats 24 h after intratracheal instillation of 500 µg Sephadex compared to the saline control group. The dose-response curves of bronchoconstriction for the two groups were virtually identical (fig. 2).

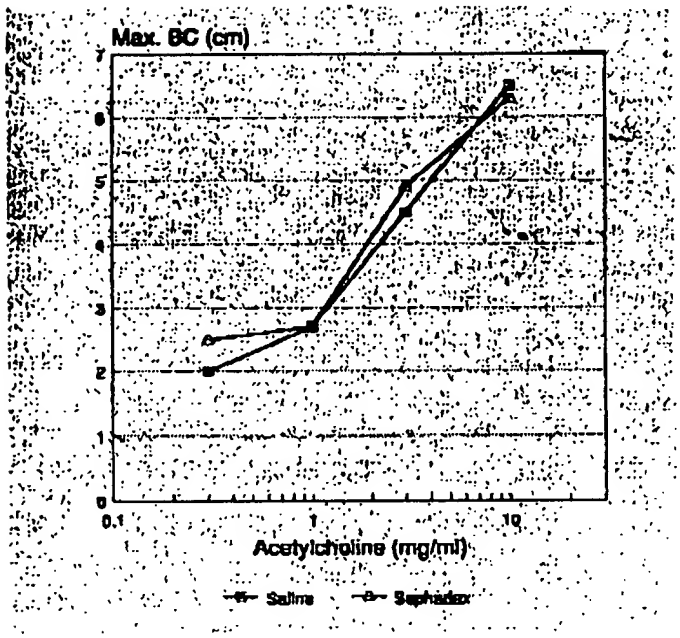

Fig. 2. Dose-response curves of maximal bronchoconstriction (max. BC) after administration of increasing doses of acetylcholine aerosol. No significant differences at any dose between Brown-Norway rats pretreated intratracheally with saline (■, n = 7) or Sephadex (Δ, n = 7). Values as mean.

Discussion

In this study we were able to demonstrate that despite massive eosinophilia of the airways and peribronchial tissue as a result of intratracheal application of Sephadex, bronchial hyperreactivity to acetylcholine aerosols was not found in Brown-Norway rats. Our results are in accordance with those of other authors, although they were obtained with different animal species and models. Sanjar et al. [23] also found no evidence of a correlation between airway eosinophilia and the degree of bronchoconstriction to ovalbumin aerosol in sensitised guinea pigs. Pretreatment with aminophylline, ketotifen or dexamethasone prevented eosinophilia but not hyperreactivity. Following subcutaneous or intraperitoneal administration of recombinant human granulocyte-macrophage colony-stimulating factor or interleukin-3 in guinea pigs, Kings et al. [24] reported eosinophilia in the BALF but found no signs of increased bronchial reactivity to i.v. histamine. Ishida et al. [25] showed that antigen-sensitised guinea pigs which were treated with an antagonist of platelet-activating factor (PAF) before multiple antigen provocation did not exhibit the airway hyperreactivity to acetylcholine aerosol shown by control animals which had received the antigen without pretreatment with the PAF antagonist. However, both groups of animals exhibited eosinophilia of the bronchial system. There are some possible explanations for the lack of a relation between airway eosinophilia and hyperreactivity in our and these animal models.

Recent experimental results increasingly suggest that it is not simply the presence of eosinophils but above all their degree of activation which is of importance for their ability to damage tissue. According to current understanding, interleukin-5, a product of activated T lymphocytes, plays a key role in the activation of eosinophils [26]. A positive correlation between the numbers of activated T cells, eosinophils and the amount of mRNA for interleukin-5 was observed in the bronchial mucosa of atopic asthmatics [27]. The number of activated eosinophils was reported to correlate with the degree of airway reactivity [28]. Furthermore, significantly elevated numbers of hypodense, activated eosinophils have been detected in the blood of asthmatics during a late-phase reaction [29]. All these observations underline the importance of activated eosinophils in the pathogenesis of chronic asthma.

Although in our animal model there was distinct eosinophilia in both the bronchial lumen and in lung tissue, little can be said about the degree of activation of these cells in the context of the investigations performed. After pretreatment with Sephadex as well as with saline only isolated lymphocytes were detected in the pulmonary tissue. In hyperreactive asthmatics clearly elevated numbers of mucosal T cells could be demonstrated [28], which might be important for the activation of eosinophils. The determination of chemiluminescence in the BALF primarily measures the phagocytosis activity of neutrophils and eosinophils. This increased by more than a factor of twenty 24 h after intratracheal application of Sephadex, correlating with the greatly elevated number of neutrophils and, in particular, eosinophils, and thus giving no indication whether eosinophil activation has taken place or not.

Although there was a significant increase in the absolute number of neutrophils in the BALF 24 h after intratracheal instillation of Sephadex, lung histology revealed only isolated neutrophils. This is probably due to the known kinetics of this cell type in response to an inflammatory stimulus: the maximum accumulation of neutrophils at the site of damage is achieved after only a few hours and then declines. The neutrophilia in the BALF is simply a reflection of the state prevailing in lung tissue a few hours earlier. The absence of distinct neutrophilia in lung tissue 24 h after intratracheal application of Sephadex in conjunction with the absence of simultaneous bron-

chial hyperreactivity could be possible evidence of the importance of this cell population for the occurrence of this symptom in the present animal model. The pathogenetic relevance in man is still discussed controversially, but distinct correlations between pulmonary neutrophilia and airway hyperreactivity have been reported in various animal models [1]. In this context it must be stressed that the histology of intratracheal Sephadex administration after 24 h only reflects certain parameters of human asthma. Asthma in man is a chronic process, often of allergic origin, while this animal model is only a short-term test with foreign body irritation of the bronchial tissue. In contrast to human asthma, granulomatous structures were observed in lung tissue in this model. The perivascular and peribronchial oedemata and the massive tissue eosinophilia, however, correspond well with the situation in asthmatics.

Recently, there have been increasing reports of a dissociation between inflammation and reactivity of the airways in man. Hargreave et al. [30] reported a connection between short-term increases in bronchial reactivity and pulmonary inflammation with mediator release, but this seems not to be definite in the case of chronic hyperreactivity in advanced asthma stages. In a noteworthy long-term study, Lundgren et al. [31] were able to show by means of biopsies of the bronchial mucosa and bronchial provocation tests that asthmatics who had been treated for 10 years with glucocorticosteroid aerosols no longer exhibited any signs of inflammatory infiltration in bronchial tissue although they were still hyperreactive to inhaled methacholine.

In summary, we were able to show in Brown-Norway rats that despite massive eosinophilia of the airways and lung tissue 24 h after intratracheal instillation of Sephadex, there was no increase in bronchial hyperreactivity to acetylcholine aerosol. Although the degree of activation of these cells is subject to speculation, it may be stated that in this animal model the absolute number of pulmonary eosinophil granulocytes does not permit positive conclusions on airway reactivity to be drawn. This is an observation which can probably also have to be applied to other animal models of asthma.

Acknowledgements

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,674,860	**$850.00**	**$0.00**	**08/317,407**	**10/07/97**	**10/03/94**	**04**	**NO**	**PAID**	**1103326018**

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PATENT NUMBER	FEE AMT	SUR CHARGE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	STAT	ATTY DKT NUMBER
5,674,860	**$2,300.00**	**$0.00**	**08/317,407**	**10/07/97**	**10/03/94**	**08**	**NO**	**PAID**	**1103326018**

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EXHIBIT F

PATENT CLAIM COVERAGE OF APPROVED PRODUCT

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
1. A medicament containing as active ingredients effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:4 to 1:60.	Symbicort 80/4.5 is a medicament that contains as its active ingredients budesonide (80 mcg[1]) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio[2] of formoterol to budesonide in Symbicort 80/4.5 is 1:17.4. Symbicort 160/4.5 is a medicament that contains as its active ingredients budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio[3] of formoterol to budesonide in Symbicort 80/4.5 is 1:34.8. Formoterol fumarate is a physiologically acceptable salt of formoterol, which has been approved by the FDA, and because it is a dihydrate, it is also a solvate. Symbicort is therefore within the scope of claim 1.
3. The medicament of claim 1 or 2 wherein the formoterol is in the form of the fumarate dihydrate.	The formoterol in Symbicort is present in the form of formoterol fumarate dihydrate. Therefore, Symbicort is within the scope of claim 3.

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[1] The abbreviation "mcg" (as used in this paper) and "μg" (as used in the subject patent) both refer to micrograms.

[2] Symbicort 80/4.5 delivers 4.5 mcg of formoterol fumarate dihydrate (formula weight 840.91; this salt comprises two molecules of formoterol per formula weight), corresponding to 0.0107 micromoles of formoterol; and 80 mcg of budesonide (formula weight 430.53), corresponding to 0.186 micromoles of budesonide. The ratio of formoterol to budesonide is therefore (0.0107):(0.186), which is 1:17.4.

[3] Symbicort 160/4.5 delivers 4.5 mcg of formoterol fumarate dihydrate (formula weight 840.91; this salt comprises two molecules of formoterol per formula weight), corresponding to 0.0107 micromoles of formoterol; and 160 mcg of budesonide (formula weight 430.53), corresponding to 0.372 micromoles of budesonide. The ratio of formoterol to budesonide is therefore (0.0107):(0.372), which is 1:34.8.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
4. A pharmaceutical composition which comprises effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:4 to 1:60, together with a pharmaceutically acceptable carrier.	Symbicort 80/4.5 is a pharmaceutical composition that contains as its active ingredients budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:17.4. Symbicort 160/4.5 is a pharmaceutical composition that contains as its active ingredients budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:34.8. The formoterol is in the form of a fumarate salt, which is a physiologically acceptable salt, and a hydrate (solvate). Both formulations of Symbicort also contain at least one pharmaceutically acceptable carrier, povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant. Therefore, Symbicort is within the scope of claim 4.
5. The pharmaceutical composition of claim 4 wherein the formoterol is in the form of the fumarate dihydrate.	The formoterol in Symbicort is present in the form of formoterol fumarate dihydrate. Therefore, Symbicort is within the scope of claim 5.
9. A medicament containing as active ingredients effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:1 to 1:60.	Symbicort 80/4.5 is a medicament that contains as its active ingredients budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:17.4. Symbicort 160/4.5 is a medicament that contains as its active ingredients budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:34.8. The formoterol is in the form of a fumarate salt, which is a physiologically acceptable salt, and a hydrate (solvate). Therefore, Symbicort is within the scope of claim 9.
11. The medicament of claim 9 or 10 wherein the formoterol is in the form of the fumarate dihydrate.	The formoterol in Symbicort is present in the form of formoterol fumarate dihydrate. Therefore, Symbicort is within the scope of claim 11.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
12. A pharmaceutical composition which comprises effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:1 to 1:60, together with a pharmaceutically acceptable carrier.	Symbicort 80/4.5 is a pharmaceutical composition that contains as its active ingredients budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:17.4. Symbicort 160/4.5 is a pharmaceutical composition that contains as its active ingredients budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:34.8. The formoterol is in the form of a fumarate salt, which is a physiologically acceptable salt, and a hydrate (solvate). Both formulations of Symbicort also contain povidone K25 USP as a suspending agent and polyethylene glycol 1000 NF as a lubricant. Therefore, Symbicort is within the scope of claim 12.
13. The pharmaceutical composition of claim 12 wherein the formoterol is in the form of the fumarate dihydrate.	The formoterol in Symbicort is present in the form of formoterol fumarate dihydrate. Therefore, Symbicort is within the scope of claim 13.
17. A method for the treatment of asthma and other inflammatory respiratory disorders which comprises administering by inhalation to a host in need of such treatment effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:4 to 1:60.	Symbicort is approved for the long-term maintenance treatment of asthma in patients 12 years of age and older. The approved labeling requires two actuations of Symbicort to be administered by inhalation twice daily, for a total of four actuations per day Symbicort 80/4.5 contains as its active ingredients budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:17.4. Symbicort 160/4.5 contains as its active ingredients budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:34.8. The formoterol is in the form of a fumarate salt, which is a physiologically acceptable salt, and a hydrate (solvate). The method of treatment of asthma by the administration of Symbicort is therefore within the scope of claim 17.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
18. The method according to claim 17, wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6-100 μg per day, and the effective amount of budesonide is 50-4800 μg per day.	The approved labeling information for Symbicort requires two actuations of Symbicort to be administered twice daily to a patient, for a total of four actuations per day. Each actuation of Symbicort 80/4.5 delivers 80 mcg of micronized budesonide and 4.5 mcg of micronized formoterol fumarate dihydrate from the inhaler actuator. Therefore, the approved labeling information for Symbicort 80/4.5 provides for administration of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 320 mcg of budesonide per day. Each actuation of Symbicort 160/4.5 delivers 160 mcg of micronized budesonide and 4.5 mcg of formoterol fumarate dihydrate micronized from the inhaler actuator. Therefore, the approved labeling information for Symbicort 160/4.5 provides for administration to a patient of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 640 mcg of budesonide per day. The method of treatment of asthma using Symbicort is therefore within the scope of claim 18.
19. The method according to claim 18 wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6-48 μg per day, and the effective amount of budesonide is 100-1600 μg per day.	The approved labeling information for Symbicort requires two actuations of Symbicort to be administered twice daily to a patient, for a total of four actuations per day. Each actuation of Symbicort 80/4.5 delivers 80 mcg of micronized budesonide and 4.5 mcg of micronized formoterol fumarate dihydrate from the inhaler actuator. Therefore, the approved labeling information for Symbicort 80/4.5 provides for administration of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 320 mcg of budesonide per day. Each actuation of Symbicort 160/4.5 delivers 160 mcg of micronized budesonide and 4.5 mcg of formoterol fumarate dihydrate micronized from the inhaler actuator. Therefore, the approved labeling information for Symbicort 160/4.5 provides for administration to a patient of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 640 mcg of budesonide per day. The method of treatment of asthma using Symbicort is therefore within the scope of claim 19.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
22. The method according to any one of claims 17, 18 and 19 wherein the administration is performed from a metered dose inhaler.	Symbicort is supplied in 10.2 g canisters which are formulated as a hydrofluoroalkane-propelled pressurized metered dose inhaler containing 120 actuations. Each actuation meters either 91/5.1 mcg or 181/5.1 mcg of the active ingredients from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg of the active ingredients from the actuator. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 22.
23. The method according to any one of claims 17, 18 and 19 wherein the formoterol is in the form of the fumarate dihydrate.	The formoterol in Symbicort is present in the form of formoterol fumarate dihydrate. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 23.
25. A method according to any one of claims 17, 18 and 19 wherein the formoterol component and the budesonide component are administered simultaneously.	Symbicort is supplied in canisters which are formulated as pressurized metered dose inhalers. Each actuation of Symbicort delivers the budesonide and the formoterol fumarate dihydrate simultaneously in the same actuation. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 25.
26. The method according to any one of claims 17, 18 and 19, wherein the physiologically acceptable salt of formoterol or the solvate thereof is administered in admixture with the budesonide.	Symbicort contains budesonide and formoterol fumarate dihydrate formulated in a single pressurized canister which contains both active ingredients. Each actuation of Symbicort meters budesonide and formoterol fumarate dihydrate in the same actuation. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 26.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
27. A method for the treatment of asthma and other inflammatory respiratory disorders which comprises administering by inhalation to a host in need of such treatment effective amounts of a physiologically acceptable salt of formoterol or a solvate thereof, and budesonide wherein the molar ratio of the formoterol component to the budesonide component is in the range from 1:1 to 1:60.	Symbicort is approved for the long-term maintenance treatment of asthma in patients 12 years of age and older. A patient inhales two actuations of Symbicort twice a day. Symbicort 80/4.5 contains as its active ingredients budesonide (80 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:17.4. Symbicort 160/4.5 contains as its active ingredients budesonide (160 mcg) and formoterol fumarate dihydrate (4.5 mcg). The molar ratio of formoterol to budesonide in Symbicort 80/4.5 is 1:34.8. The formoterol is in the form of a fumarate salt, which is a physiologically acceptable salt, and a hydrate (solvate). Therefore, the method of treatment of asthma by the administration of Symbicort is within the scope of claim 27.
28. The method according to claim 27, wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6-100 μg per day, and the effective amount of budesonide is 50-4800 μg per day.	The approved labeling information for Symbicort requires two actuations of Symbicort to be administered twice daily to a patient, for a total of four actuations per day. Each actuation of Symbicort 80/4.5 delivers 80 mcg of micronized budesonide and 4.5 mcg of micronized formoterol fumarate dihydrate from the inhaler actuator. Therefore, the approved labeling information for Symbicort 80/4.5 provides for administration of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 320 mcg of budesonide per day. Each actuation of Symbicort 160/4.5 delivers 160 mcg of micronized budesonide and 4.5 mcg of formoterol fumarate dihydrate micronized from the inhaler actuator. Therefore, the approved labeling information for Symbicort 160/4.5 provides for administration to a patient of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 640 mcg of budesonide per day. The method of treatment using Symbicort is therefore within the scope of claim 28.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
29. The method according to claim 28 wherein the effective amount of the physiologically acceptable salt of formoterol or solvate thereof is 6-48 μg per day, and the effective amount of budesonide is 100-1600 μg per day.	The approved labeling information for Symbicort requires two actuations of Symbicort to be administered twice daily to a patient, for a total of four actuations per day. Each actuation of Symbicort 80/4.5 delivers 80 mcg of micronized budesonide and 4.5 mcg of micronized formoterol fumarate dihydrate from the inhaler actuator. Therefore, the approved labeling information for Symbicort 80/4.5 provides for administration of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 320 mcg of budesonide per day. Each actuation of Symbicort 160/4.5 delivers 160 mcg of budesonide and 4.5 mcg of formoterol fumarate dihydrate from the inhaler actuator. Therefore, the approved labeling information for Symbicort 160/4.5 provides for administration to a patient of a total of 18 mcg of formoterol fumarate dihydrate per day and a total of 640 mcg of budesonide per day. The method of treatment of asthma using Symbicort is therefore within the scope of claim 29.
32. The method according to any one of claims 27, 28 and 29 wherein the administration is performed from a metered dose inhaler.	Symbicort is supplied in 10.2 g canisters which are formulated as a hydrofluoroalkane-propelled pressurized metered dose inhaler containing 120 actuations. Each actuation meters either 91/5.1 mcg or 181/5.1 mcg of the active ingredients from the valve and delivers either 80/4.5 mcg or 160/4.5 mcg of the active ingredients from the actuator. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 32.
33. The method according to any one of claims 27, 28 and 29 wherein the formoterol is in the form of the fumarate dihydrate.	The formoterol in Symbicort is present in the form of formoterol fumarate dihydrate. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 33.

Applicable Claims of U.S. Patent No. 5,674,860	Manner in Which Each Claim Reads on the Approved Product or Method of Using the Approved Product
35. The method according to any one of claims 27, 28 and 29 wherein the formoterol component and the budesonide component are administered simultaneously.	Symbicort is supplied in canisters which are formulated as pressurized metered dose inhalers. Each actuation of Symbicort delivers the budesonide and the formoterol fumarate dihydrate simultaneously in the same actuation. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 35.
36. The method according to any one of claims 27, 28 and 29, wherein the physiologically acceptable salt of formoterol or the solvate thereof is administered in admixture with the budesonide.	Symbicort contains budesonide and formoterol fumarate dihydrate formulated in a single pressurized canister. Each actuation of Symbicort meters budesonide and formoterol fumarate dihydrate in the same actuation. Therefore, the method of treatment of asthma by administration of Symbicort is within the scope of claim 36.

CHRONOLOGY OF SIGNIFICANT ACTIVITIES: IND 63,394 AND NDA 21-929		
Application No.	**Date**	**Description**
IND 63,394	28-Feb-01	Symbicort HFA pMDI Briefing Package: AZ's proposed development program for Symbicort HFA pMDI
IND 63,394	20-Apr-01	Symbicort HFA pMDI Briefing Package (Second): Updated alternate scenario to the Development Program presented in the February 28, 2001 Briefing Package
IND 63,394	3-May-01	Pre-IND Meeting (FDA Meeting Minutes received 01-Jun-2001)
IND 63,394	15-Jun-01	AZ submission: Briefing Package and Meeting Request: Revised Clinical Program using Pulmicort HFA pMDI (FDA response received on 31-Jul-2001)
IND 63,394	**5-Oct-01**	**IND filed**
IND 63,394	16-Jan-02	Briefing Document: for EOP2 Meeting
IND 63,394	2-Apr-02	Asthma Clinical End of Phase 2 Meeting with the FDA (FDA Meeting Minutes received 01-Apr-2003)
IND 63,394	4-Apr-02	CMC End of Phase2 Meeting with the FDA (FDA Meeting Minutes received 01-Apr-2003)
IND 63,394	24-Apr-02	Agency's CMC Comments to the CMC Briefing Document submitted on January 16, 2002
IND 63,394	13-Jun-02	Briefing Document: Development of a Dose Counter for the Symbicort pMDI product
IND 63,394	26-Sep-02	FDA Face-to-Face Meeting with AZ re: Clarify issues presented in the 13 Jun-2002 Briefing Document (FDA Meeting Minutes received on 17-Oct-2002)
IND 63,394	8-Apr-03	Type C Meeting: Regarding RAQ Pediatric Exclusivity labeling, progress on AZ's Pulmicort TBH M3 product, Symbicort clinical programs and progress on Pulmicort Respules Phase 4 commitments (FDA Meeting Minutes received 16-Apr-2003)
IND 63,394	6-May-04	Request for pre-NDA meeting and Briefing Package for Asthma pre-NDA meeting
IND 63,394	28-Jun-04	Clinical Asthma pre-NDA meeting (FDA Meeting Minutes received 28-Jul-2004 with corrections received on 14-Sep-2004)
IND 63,394	27-Sep-04	Briefing Package for CMC pre-NDA meeting (FDA responses received 29-Oct-2004)
IND 63,394	1-Nov-04	CMC Pre-NDA Meeting (FDA Meeting Minutes received on 05-Jan-2005)
IND 63,394	12-May-05	CMC Briefing Document submitted
IND 63,394	22-Jun-05	CMC Advice Meeting (FDA Meeting Minutes received on 31 August 2005)
NDA 21-929	**23-Sep-05**	**NDA filed**

Application No.	Date	Description
NDA 21-929	19-Oct-05	FDA Telephone contact: FDA requesting information about synthetic scheme and approved specifications and manufacturing sites.
NDA 21-929	21-Oct-05	Response to the FDA Telephone Contact from 19-Oct-05
NDA 21-929	31-Oct-05	FDA Telephone contact: FDA requesting samples and additional information on manufacturing sites.
NDA 21-929	2-Nov-05	Response to the 31-Oct-05 FDA Telephone Contact regarding samples and additional information on manufacturing sites.
NDA 21-929	7-Nov-05	FDA Telephone contact: FDA requesting additional CMC information (P.2, standard vs. Sh mouthpiece/actuators, stability for leachables)
NDA 21-929	8-Nov-05	Response to FDA Telephone Contact on 07-Nov-05
NDA 21-929	28-Nov-05	FDA Telephone contact: FDA information request on Symbicort name and 90-day meeting
NDA 21-929	29-Nov-05	AZ Meeting request: with FDA: Request for Ninety-day meeting
NDA 21-929	29-Nov-05	Incoming FDA fax: 716 and 717 stats questions
NDA 21-929	5-Dec-05	Teleconference (SAS issues) (FDA Meeting Minutes received on 27-Dec-2005)
NDA 21-929	6-Dec-05	FDA fax: Acknowledgement letter and filing review letter
NDA 21-929	8-Dec-05	Submission of samples
NDA 21-929	13-Dec-05	FDA Teleconference with AZ regarding clarification of 74-day letter CMC issues (FDA Meeting Minutes received on 10-Jan-2006)
NDA 21-929	15-Dec-05	Response to FDA request for info: Nomenclature
NDA 21-929	15-Dec-05	AZ response to November 29 fax (SAS info)
NDA 21-929	19-Dec-05	AZ Response to 74-day letter response (Gunkel) potential review issue
NDA 21-929	27-Dec-05	AZ's 74-day letter response (CMC issues) and request for teleconference
NDA 21-929	11-Jan-06	FDA Telecon re: Dec. 27 submission (FDA meeting Minutes received on 09-Feb-2006)
NDA 21-929	30-Jan-06	AZ submission of full response to Item 2 from 74-day letter
NDA 21-929	19-Jan-06	4MSU submitted
NDA 21-929	3-Mar-06	FDA Fax: Information Request Letter: Clinical and Pharm/Tox questions arising from 5 month mid-cycle review meeting.
NDA 21-929	8-Mar-06	FDA Fax: Information Request Letter: CMC comments and information requests (1st CMC IRL request).
NDA 21-929	13-Mar-06	Letter from AZ to FDA, re: 90-day meeting (denied request and reason why)
NDA 21-929	16-Mar-06	Meeting Request: Clarification of CMC IRL dated March 8, 2006
NDA 21-929	17-Mar-06	Response to March 3, 2006 IRL
NDA 21-929	28-Mar-06	CMC Type C Teleconference (FDA Meeting Minutes received on 25-Apr-2006)
NDA 21-929	4-Apr-06	FDA Fax regarding March 17, 2006 Response to IRL: Fax provided 2 options for reanalysis of rat lung histopathology findings: convene an independent pathology working group or complete a blinded reanalysis of the rat lung slides by an independent histopathologist

Application No.	Date	Description
NDA 21-929	12-Apr-06	FDA Fax: Information Request Letter: Additional CMC comments and information requests (2nd CMC IRL Request)
NDA 21-929	13-Apr-06	AZ's Response to March 8th CMC Information Request Letter (70 of 76 responses; 6 responses outstanding)
NDA 21-929	26-Apr-06	AZ's Response to FDA: Providing Information from the Pharmacology/Toxicology Section: Independent review of rat lung samples by an independent histopathologist.
NDA 21-929	27-Apr-06	AZ's Response to (Outstanding) Questions from the March 8th CMC IRL: 2nd Response (5 questions outstanding)
NDA 21-929	28-Apr-06	FDA's Response to AZ's April 19th Request for clarification of April 12 CMC IRL
NDA 21-929	28-Apr-06	FDA Fax: Information Request Letter for Studies 716 and 717 (1st Clinical IRL Request)
NDA 21-929	4-May-06	Fax from the FDA: Information Request Letter: CMC (3rd CMC IRL Request)
NDA 21-929	9-May-06	Response to FDA Information Request Facsimile (28 April 2006) for NDA 21-929 for SYMBICORT® Pressurized Metered Dose Inhaler
NDA 21-929	10-May-06	AZ's Response to (more outstanding) Questions from the March 8th and April 12th CMC letters (11 of 16 responses completed; 5 responses outstanding)
NDA 21-929	10-May-06	FDA Fax: Clinical IRL: 2 questions related to Study SD-039-0715 (2nd Clinical Request)
NDA 21-929	15-May-06	CMC responses to 5 of the 9 issues raised in the 04 May CMC IRL
NDA 21-929	15-May-06	Electronic Response to FDA Information Request Facsimile (10 May 2006) for NDA 21-929 for SYMBICORT® Pressurized Metered Dose Inhaler
NDA 21-929	24-May-06	FDA Fax: Information Request Letter: CMC (4th CMC IRL Request)
NDA 21-929	31-May-06	CMC IRL Response: CMC responses to 5 of the remaining issues raised in the first three CMC IRLs
NDA 21-929	1-Jun-06	Response to 4th CMC IRL Request
NDA 21-929	14-Jun-06	Response to portions of 1st, 2nd, 3rd and 5th CMC IRLs (1st and 2nd CMC IRLs still have outstanding issues).
NDA 21-929	8-Jun-06	FDA Fax: Information Request Letter: CMC (5th CMC IRL Request) FDA requesting we revise the proposed specification for dose content uniformity
NDA 21-929	14-Jun-06	Response to portions of 1st, 2nd, 3rd and 5th CMC IRLs (1st and 2nd CMC IRLs still have outstanding issues).
NDA 21-929	19-Jun-06	Response to FDA Request for Information/ Carton Container Labels
NDA 21-929	21-Jun-06	FDA Telephone Contacts: FDA Request for Information re: labeling
NDA 21-929	22-Jun-06	Fax from the FDA: Preliminary Review Labeling Comments
NDA 21-929	27-Jun-06	Labeling Response to 22-Jun-06 fax
NDA 21-929	29-Jun-06	FDA Asthma Labeling Teleconference
NDA 21-929	5-Jul-06	Fax from the FDA: Information Request Letter: CMC (6th CMC IRL Request)
NDA 21-929	10-Jul-06	Fax from the FDA: Preliminary Labeling Comments for the proposed Medication Guide submitted on 27 June 2006

Application No.	Date	Description
NDA 21-929	12-Jul-06	Response to FDA Preliminary Labeling Comments
NDA 21-929	12-Jul-06	Response to the 6th CMC IRL
NDA 21-929	13-Jul-06	FDA Telephone Contact: Request: In regards to the AC Actuator, clarify how it is determined that these permitted contaminants will not harm the user, or the functionality of the product.
NDA 21-929	17-Jul-06	Response to FDA Request dated 13 July 2006 (re: AC Actuator)
NDA 21-929	17-Jul-06	FDA Fax: Additional Preliminary Labeling Comments regarding the PI and the Medication Guide dated 11 July 2006.
NDA 21-929	18-Jul-06	AZ Response to July 17 2006 Labeling Comments
NDA 21-929	19-Jul-06	FDA Asthma Labeling Teleconference
NDA 21-929	19-Jul-06	Labeling Response to the FDA (PI and MedGuide) incorporating comments received during 19 July 2006 Teleconference
NDA 21-929	20-Jul-06	Labeling Response to the FDA (Carton and Container labels) incorporating comments received during 19 July 2006 Teleconference
NDA 21-929	20-Jul-06	FDA Fax: Additional Labeling Comments regarding the PI and the Medication Guide
NDA 21-929	20-Jul-06	Labeling Response to the FDA (PI and MedGuide) incorporating comments received from a FDA fax dated 20 July 2006
NDA 21-929	21-Jul-06	FDA Fax: Approval Action Letter for Symbicort MDI in Asthmatic patients 12 years of age and older